Drug Use and Misuse in the Mountains. An UIAA MedCom-Consensus Guide for Medical Professionals

Enrico Donegani[1], Peter Paal[2], Thomas Küpper[3], Urs Hefti[4], Buddha Basnyat[5], Anna Carceller[6], Pierre Bouzat[7], Rianne van der Spek[8], David Hillebrandt[9]

[1] Enrico Donegani, MD, Professor of Cardiology, Cardiac Surgery, Thoracic Surgery, Mountain Medicine. Consultant in Cardiovascular Surgery, Sabah Al-Ahmed Cardiac Center, Al-Amiri Hospital, Kuwait (State of Kuwait). Royal Residence, apt.45, Benid Al Gar, Block 1, Street 88, Kuwait (State of Kuwait). Tel +965 99336938. E-mail donegani.enrico@gmail.com

[2] Peter Paal, MD, PD, MBA, EDAIC, EDIC; Consultant in Anaesthesia and Intensive Care Medicine; Department of Anaesthesiology and Critical Care Medicine, Innsbruck University Hospital, Innsbruck, Austria and the Barts Heart Centre, St Bartholomew's Hospital, West Smithfield, Barts Health NHS Trust. Queen Mary University of London, London, United Kingdom. Perioperative Medicine, Office 10 1st floor, St Bartholomew's Hospital, KGV Building, London, EC1A 7BE. Tel +44 (0) 7492 051609. peter.paal@icloud.com

[3] Prof. Thomas Küpper, MD, PhD, Professor for Travel Medicine, High Altitude Medicine, Sports Medicine, Aviation Medicine and Occupational Medicine; Institute of Occupational & Social Medicine, RWTH Aachen University, Pauwelsstr. 30, 52074 Aachen, Germany, Tel +49 2418088880, tkuepper@ukaachen.de

[4] Urs Hefti, MD, Consultant in Orthopedic and Trauma Surgery, Swiss Sportclinic, Sempachstrasse 33, 3014 Bern, Switzerland, Tel. +41796928215, urshefti@bluewin.ch .

[5] Buddha Basnyat, MD, MSc, FACP, FRCP (Edinburgh); Oxford University Clinical Research Unit-Nepal. Nepal International Clinic, and Himalay Rescue; NIC, Lal Durbar, GPO Box 3596. Kathmandu, Nepal. Phone 97714434642, buddhabasnyat@gmail.com

[6] Anna Carceller; Professional Sports Medicine School, University of Barcelona. Instituto de Medicina de Montaña y del Deporte (IMMED). Federació d'Entitats Excursionistes (FEEC). Spain; medical@feec.cat

[7] Pierre Bouzat, MD, PhD; Department of Anesthesiology and Critical Care, Grenoble University Hospital, 38000 Grenoble, France; Grenoble Alps University, 38000 Grenoble, France, and Grenoble Neuroscience Institute, INSERM U1236, 38000 Grenoble, France; Tel +33 4 56 52 05 89; fax +33 4 56 52 05 98; PBouzat@chu-grenoble.fr

[8] Rianne van der Spek, MSc (MD, PhD student) Department of Endocrinology and Metabolism, Academic Medical Center Amsterdam, University of Amsterdam, Meibergdreef 9, 1105AZ Amster-

dam, The Netherlands; Tel +31616 930320, r.d.vanderspek@amc.uva.nl / riannevdspek@gmail.com

[9] David Hillebrandt, MB, BS (Lond), FIMC RCS (Edin), Dip Trav Med (Glas), Dip Mtn Med (UIAA and Leics); President UIAA Medical Commission, UIAA Office, Monbijoustrasse 61, Postfach CH-3000, Bern 23, Switzerland. Home/Office: Derriton House, Derriton, Holsworthy, Devon. EX22 6JX, England. Tel + 44 (0) 1409 253814; dh@hillebrandt.org.uk

Corresponding author: David Hillebrandt, MB, BS (Lond), FIMC RCS (Edin), Dip Trav Med (Glas), Dip Mtn Med (UIAA and Leics); President UIAA Medical Commission, UIAA Office, Monbijoustrasse 61, Postfach CH-3000, Bern 23, Switzerland. Home/Office: Derriton House, Derriton, Holsworthy, Devon. EX22 6JX, England. Tel + 44 (0) 1409 253814; dh@hillebrandt.org.uk

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Abstract

Aims: The aim of this review is to inform mountaineers about drugs commonly used in mountains. For many years drugs have been used to enhance performance in mountaineering. It is the UIAA (International Climbing and Mountaineering Federation - Union International des Associations d'Alpinisme) Medcom's duty to protect mountaineers from possible harm caused by uninformed drug use. The UIAA Medcom assessed relevant articles in scientific literature, and peer-reviewed studies, trials, observational studies and case series to provide information for physicians on drugs commonly used in the mountain environment. Recommendations were graded according to criteria set by the American College of Chest Physicians.

Results: Prophylactic, therapeutic and recreational uses of drugs relevant to mountaineering are presented with an assessment of their risks and benefits.

Conclusions: If using drugs not regulated by the World Anti Doping Agency (WADA) individuals have to determine their own personal standards for enjoyment, challenge, acceptable risk and ethics. No system of drug testing could ever, or should ever, be policed for recreational climbers. Sponsored climbers or those who climb for status need to carefully consider both the medical and ethical implications if using drugs to aid performance. In some countries (e.g. Switzerland and Germany) administrative systems for mountaineering or medication control dictate a specific stance, but for most recreational mountaineers any “rules” would be unenforceable and have to be a personal decision but should take into account the current best evidence for risk, benefit and sporting ethics.

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Running title: Drug Use and Misuse in the Mountains

INTRODUCTION

Since the earliest days of recreational mountaineering climbers have tried various drugs to enhance their experiences. Whisky has been used at the end of a hard Scottish mountain day (Ogilvie, 1976), supplementary oxygen at altitude for Everest expeditions since 1922 (Bruce, 1923), methamphetamine to aid endurance (Buhl, 1998), cannabis and psycho-stimulants on big wall bivouacs (Mortimer and Rosen, 2014), cocaine for solo climbing (Perrin, 1978), drug cocktails to “aid” acclimatization (Freer, 2015), acetazolamide to facilitate fast ascents of Kilimanjaro to minimize the daily mountain fee despite the risks involved (Küpper et al., 2010), and drug use on Mont Blanc (Robach et al., 2016).

In 2004 the topic of drug use in the mountains was informally discussed at the International Climbing and Mountaineering Federation (UIAA) Medical Commission (MedCom) meeting in Teheran and at the Aachen meeting in 2005 it was formally acknowledged that the Management committee of the UIAA agreed that the topic fell under the remit of the UIAA MedCom. The UIAA MedCom has over 50 members from over 25 countries representing views, which cross all geographical, political, cultural, religious and historical boundaries. Achieving a consensus is not easy, especially when it involves the ethics of our sport, so it was not until our meeting in Sweden in 2011 that we agreed that an advice paper was needed and should be based on the following principles:

1) World Anti Doping Agency (WADA) regulation was fully accepted for all formal competitive climbing or mountaineering (competitive sport climbing either indoor or outdoor, ice climbing competitions and ski mountaineering competitions)
2) Formal regulation of all recreational mountaineers is impossible
3) A policy of encouraging honesty with one’s peers regarding use of any artificial aids on climbs should be encouraged. This includes drug use as much as bolts and fixed ropes
4) With much misinformation available on drug use our aim must be to protect climbers and mountaineers from harm caused by ill-advised drug use. This is best achieved by supplying evidence based guidance

Drug Use and Misuse in the Mountains

This agreement paved the way for our first advice paper on drug use and misuse in the mountains which was written for a lay audience and, after some controversy, was adopted by the UIAA and published on their website in 2014 with its more detailed introduction and history (UIAA 2016). It immediately became apparent that a more technical version of the paper was needed for medical professionals advising mountaineers and work on this paper has taken a further two years.

METHODS

The UIAA MedCom convened an expert group to develop evidence-based guidelines for drug use and misuse in mountains. Drugs included in this work were selected according to their importance in mountain medicine due to their action on general health, preventing and treating acute altitude illness or physical and psychological performance enhancing effects.

A literature review was performed using PubMed, Current Contents, Embase (DIMDI) Medline and bibliographies of retrieved articles. Search terms including i) the pharmacological agent alone or ii) in combination with the search keywords (i.e. “acute mountain sickness” “altitude”, “doping”, “exercise”, “mountain medicine”, “sport”) were used. Randomized controlled trials, observational studies, case series and case reports limited to humans were included in this work. The article was compiled by one author (ED) and revised by the co-authors. Recommendations were developed by consensus and graded, based on available evidence strength and quality using the grading system of the American College of Chest Physicians (Table 1) (Guyatt et al., 2006). The reference list was the last time updated with PubMed on May 15th 2016, references were included based on the pertinence to this article. When no studies existed to provide evidence, the recommendations were based on experience and knowledge of the expert group. Finally the article was discussed and approved by the UIAA MedCom, using a consensus approach to develop recommendations. Conclusions of the authors were considered in the formulation of our conclusions to provide a substratum of information on the various problems and their management. Any discrepancy or heterogeneity between results from different studies on the same drug or inconclusive studies were evaluated and discussed and resolved by UIAA MedCom**.**

RESULTS

Several hundred articles including randomized controlled trials, review articles, observational studies, case series and single reports were identified, and 321 were deemed relevant, and included in this study. The primary purpose of this analysis was to determine the medical efficacy and the level of evidence of each drug commonly used for i) the prevention and ii) treatment of high-altitude illness, assessing risks and benefits. Secondary purpose was to determine the state of knowledge on the effects of peculiar drugs generally used on improving physical and cognitive performance in the mountains.

DISCUSSION

1. ALCOHOL

Ethanol (ethyl alcohol) is an intoxicating ingredient found in many beverages. Its toxicity is largely caused by its primary metabolite, acetaldehyde (systematic name ethanal) and secondary metabolite, acetic acid (Caballeria, 2003). Ethanol diminishes muscular performance by inhibiting sarcolemmal calcium channel actions thereby impairing excitation-contraction coupling (Cofan and others 2000).

Alcohol has detrimental effects on exercise performance, depending on dose, individual characteristics (e.g. sex, age, metabolic activity, consumption habits) and on the sort of physical activity undertaken (Pesta et al., 2013). While light drinking the night before will not significantly influence physical activity the following morning, heavier drinking severely affects aerobic capacity increasing heart rate and reducing maximal oxygen consumption (VO_2max) (Bond et al., 1983; Vella and Cameron-Smith, 2010). The detrimental effects on aerobic performance are dose-dependent with a threshold of 20 mmol/L, upon which the effects become substantial (Bond et al.,1983).

Alcohol intoxication impairs the myocardium, resulting in a decreased end-systolic pressure-dimension slope and reduced velocity of myocardial fiber shortening (Barnes et al.,2010b). Alcohol also impairs recovery following exercise by compromising glycogen re-synthesis after prolonged effort, most likely by suppressing the **m**ammalian **t**arget **o**f **r**apamycin (mTOR) pathway, a serine/threonine protein kinase that regulates cell growth (Pesta et al.,2013).

Alcohol consumption is associated with the deterioration of psychomotor skills and delayed recovery after strenuous exercise (Barnes et al.,2010a). Athletes who consume alcohol at least once a week almost double their risk of injury compared with non-drinkers, but the exact mechanisms are unknown (O'Brien and Lyons, 2000). It also interferes with the body’s ability to recover from injury: 1g/kg body weight alcohol consumption significantly decreases isokinetic torque production (40-44%) in quadriceps 36 hours into recovery (Barnes et al.,2010b; Gutgesell and Canterbury, 1999; O'Brien and Lyons, 2000).

At altitude: The theoretical "benefit" of the glass of red wine prior to or during the ascent to ameliorate physical performance may be related to the inhibition of release of the potent pulmonary artery vasoconstrictor, endothelin-1 (ET-1) and increased generation of reactive oxygen species (superoxide anion, O_2-) by wine polyphenols, especially resveratrol, which total content is greater in red wines than in white, rose and distilled spirits. The ingestion of one glass (100 mL) of standard dry red wine (approx. 12% alcohol) provides 12 grams of ethanol. This "low-dose" ethanol may inhibit increased vasoconstricting endothelin 1 (ET-1) synthesis and superoxide anion generation in response to altitude hypoxia. The effect of red wine may be both via ethanol itself and by many of the polyphenols such as resveratrol that it also contains. Especially red wine is a rich source of polyphenols and their ability to enhance endothelial-type nitric oxide (NO) synthase (eNOS) expression in humans has been demonstrated (Wallerath et al., 2005). Low concentrations of alcohol induce increased release of NO from the human endothelial cells due to activation of eNOS, which exerts important effects in physiological blood flow and blood pressure, with vasoprotective effects preventing pathological vascular damage (Toda and Ayajiki, 2010). Perhaps this explains the preference of some mountain climbers for that "glass of red wine" that makes them "feel better" (Schafer and Bauersachs, 2002).

The effects of excessive intake of alcohol may be exacerbated by other altitude-related factors such as dehydration, sleep disorders, fatigue and cold and, in turn, its diuretic effect may worsen dehydration. Alcohol has marked effects on judgment and decision-making. It also reduces reflex times, interferes with balance motor control and coordination and also impairs the ability to assess and manage risk. Its slow degradation means that the effects persist well beyond a traditional alpine start: also small amounts of blood alcohol concentration of 0.03 g/L can persist for a substantial period of time after the acute effects of alcohol impairment disappear (Roeggla et al.,1995).

Doping: Alcohol (ethanol) is only prohibited *in-competition* in some sports (e.g. air sports, archery, automobile, karate, motorcycling, power-boating). Detection is conducted by blood or breath gas analysis. The doping violation threshold is 0.10 g/L on blood samples (WADA 2016b).

Conclusions: The American College of Sports Medicine concludes that acute alcohol consumption adversely affects psychomotor skills and exercise performance depending on dose, age and metabolic activity (American Heart Association Nutrition and others, 2006). Ethanol may slow post-exercise recovery by inhibiting protein synthesis and increases the risk of injury during exercise by reducing decision-making capability, reflex times and balance (Barnes et al.,2010a; Haugvad et al.,2014; Pesta et al.,2013). A possible theoretical beneficial effect of moderate consumption of red wine in altitude is that it may help to prevent or ameliorate symptoms of high altitude pulmonary edema (HAPE) by inhibition of ET-1synthesis (Fellermeier et al.,2001).

Recommendations: Excessive intake of alcohol should be avoided before and during medium to high grade exercise in mountains as it will exacerbate fitness debilitating factors (e.g. dehydration, hypothermia), reduce exercise performance, delay recovery, and increase the risk of injury. Recommendation Grade: 1A

2. ANABOLIC AGENTS: ANDROGENIC STEROIDS

Anabolic steroids, technically known as anabolic-androgenic steroids, are drugs structurally related to the cyclic steroid ring system and synthetic derivatives of the male hormone testosterone.

Generic names include **ANDROSTENEDIONE, CLOSTEBOL, METHASTERONE, NANDROLONE, 1-TESTOSTERONE.**

Anabolic-androgenic steroids have two different, but overlapping effects. Firstly, they are *anabolic,* which means they increase protein synthesis from amino acids, appetite, bone remodelling and growth. The anabolic effect also stimulates erythropoiesis by increasing renal production of erythropoietin and by exerting an effect on bone marrow stem cell division. Secondly, these steroids are *androgenic* affecting the development and maintenance of masculine characteristics (Thein et al.,1995). Anabolic-androgenic steroids are used therapeutically to stimulate bone marrow growth in aplastic anaemia, in children with growth failure, to stimulate muscle growth, to treat chronic wasting conditions, such as with cancer and AIDS and to treat gender dysmorphia by producing secondary male characteristics. They are also given to boys with extreme puberty delay, and to men with low levels of testosterone as a replacement therapy (1990; Shahidi, 2001). Short- and long-term anabolic-androgenic steroid abuse can lead to aggression, violence and irrational behaviour, which may persist for months after withdrawal. Cardiovascular risk factors include elevation of blood pressure, depression of serum HDL and an increase in cholesterol levels. Cardiac hypertrophy is associated with secondary changes in cardiac metabolism, which contribute to cardiac dysfunction, and can progress to heart failure. Alterations in connective tissue structure induced by anabolic-androgenic steroids therapy, has been associated with weakening of tendon strength. Mood disturbances (e.g. depression, hypo-mania, psychotic features) are likely to be dose and drug dependent (Kutscher et al.,2002; Maravelias et al.,2005; Shahidi, 2001).

Use in sport: Anabolic-androgenic steroids can benefit athletic performance. Short-term administration can increase strength and bodyweight, attributed to an increase of the lean body mass. Although anabolic-androgenic steroids administration may affect erythropoiesis and haemoglobin concentration no effect on endurance performance was observed (Anonymous, 1990; Powers, 2005; Urhausen et al.,2003). The serious adverse effects of anabolic-androgenic steroids are dependant on dose, duration of use and individual genetic factors (Friedl, 2000; Wilson, 2008; Hartgens and Kuipers, 2004; Luijkx et al.,2013).

At altitude: The psychological side effects reported by studies include sleeplessness, increased irritability, depression, change in mental attitude, psychotic symptoms, and feelings of euphoria and grandiosity (Tabin and McIntosh, 2001), and these can have fatal consequences. No governing body monitors recreational climbers for drug use although anabolic-androgenic steroids have been and are being used in the preparation of expeditions and hard rock climbs. Several famous rock climbers admit to using anabolic-androgenic steroids to speed their recovery from injury or to improve performance (Tabin and McIntosh, 2001) .

Doping: Anabolic-androgenic steroids are banned by virtually every sporting organisation. The WADA includes all anabolic-androgenic steroids and precursors and all hormones and related substances at all times, both *in*- and *out-competition* (WADA, 2016b).

Conclusions: The multiple adverse effects seen at sea level may be even more pronounced at altitude and interfere with the diagnosis of high altitude cerebral edema (HACE). Their use is contra-indicated.

Recommendations: Anabolic-androgenic steroids should not be used at any time by any mountaineer. Recommendation Grade: 1B.

3. β_2- ADRENERGIC AGONISTS

INHALED β_2-AGONISTS AND SPORT

A review performed by Kindermann in 2006 on the use of inhaled β_2-agonists (studies using Salmeterol, Formoterol, Orterbutaline and Salbutamol) in non asthmatic competitive athletes revealed that there are no performance enhancing effects and no ergogenic potential of these agents in normoxia (Kindermann and Meyer, 2006). No data exist about possible ergogenic effects in hypoxia. A number of factors can induce an acute asthmatic attack in predisposed athletes including exposure to pollen, dust, chemical particles, viral infections and psychological stress (Helenius et al.,1998; Pierson et al.,1986). Physical exercise may give rise to specific “exercise induced asthma” (Tikkanen and Helenius, 1994). Inhalation of large volumes of cold, dry air with resultant bronchial oedema adds to the problem so athletes participating in winter sports are at increased risk (Heir and Oseid, 1994). Currently all β_2-agonists are prohibited by WADA *in*- and *out-competition*, with the exception of Formoterol, Salbutamol, Salmeterol and Terbutaline when inhalated to prevent and treat asthma and "exercise induced asthma". Some β_2-agonists (i.e. Salmeterol and Salbutamol) have received interest in the prevention and treatment of HAPE due to their ability to enhance alveolar clearing of the fluid.

Generic Name**: SALMETEROL**

<u>**At altitude**</u>: Clinical experience with Salmeterol at high altitude is limited. In the one randomized, placebo-controlled study, the inhaled long-acting β_2-adrenergic agonist Salmeterol at 2.5 times the normal dosing decreased the incidence of HAPE by 50% in *susceptible* individuals (Sartori et al.,2002, Luks et al. 2014). The theoretical benefit proposed by Sartori et al. (Sartori et al.,2002) occurs through changes in pulmonary transepithelial sodium transport. The tightening of the alveolo-capillary barrier, the direct lowering of pulmonary artery pressure, the indirect hypoxic ventilatory stimulation and increased nitric oxide production may also explain the beneficial effects in the reduction in the incidence of HAPE (Bartsch and Mairbaurl, 2002; Basnyat, 2002; Vivona et al.,2001). Although this finding requires confirmation, this agent is considered useful and convenient in the prevention of HAPE and, by extension possibly for treatment as well (Dunin-Bell and Boyle, 2009; Hackett and Roach, 2001; Sartori et al.2002).

Wilderness Medical Society Consensus Guidelines now suggest that Salmeterol used in high doses close to the toxic level may help in the prevention of HAPE in susceptible individuals if combined with Nifedipine (Luks et al.,2014). At high doses, the drug may present important side effects (headache, hypertension, tachycardia, muscular cramps, nasal congestion, tremor) (Hackett and Roach, 2001) and it remains unclear whether its possible benefits outweigh the risks compared with Nifedipine alone.

<u>**Doping**</u>: Salmeterol is not prohibited by the Antidoping WADA Code when taken by inhalation in accordance with the manufacturers' recommended therapeutic regime (WADA, 2016b).

Conclusions: Salmeterol can be used as a second line therapy in the prevention of HAPE. With no scientific evidence some mountaineers have assumed that Salmeterol may also increase physical performance, but evidence of improved performance is lacking (Carlsen et al.,1997; Sue-Chu et al.,1999).

Generic Name: **SALBUTAMOL (ALBUTEROL)**

Salbutamol improves muscle weight in animals, and anecdotal reports hypothesise that it might be an alternative to Clenbuterol for purpose of fat burning and muscle gain but other studies contradict these findings (Caruso et al.,2005).

At altitude: Salbutamol has not been studied for the prevention or treatment of HAPE. Only anecdotal experiences in Himalayas using Salbutamol inhalers or nebulizers for the treatment of patients with HAPE indicate an increase in the pulse-oximeter reading after the administration of the drug (Basnyat, 2002). As Salbutamol should function similarly to Salmeterol, this agent could be considered for the prevention and treatment of HAPE (Hackett and Roach, 2001)

Debilitating dry cough is a frequent problem in subjects travelling to high altitude. Bakewell and Coll showed that inhaled Salbutamol twice daily may prevent high altitude cough (Bakewell et al.,1999).

Doping: Salbutamol is not prohibited by the Antidoping WADA Code. When taken by inhalation in accordance with the manufacturers’ recommended therapeutic regime (maximum 1600 μg over 24 hours) (Berges et al.,2000; Nichols, 2004), overall performance is not improved (Koch et al.,2015).

Conclusions: Because of contradictory results and limited experience at altitude, its use is not recommended by UIAA MedCom.

Generic Name**: CLENBUTEROL**

Clenbuterol induces skeletal muscle growth through mTOR-dependent protein synthesis, with an increase in size of muscle fibre cells (Wong and others 1998). In terminal heart failure patients, left ventricular assist device support combined with high-dose Clenbuterol therapy produces maximal reverse remodeling by the induction of physiological cardiac hypertrophy (Hon and Yacoub 2003). As a β_2 sympathomimetic, Clenbuterol increases aerobic capacity, central nervous system stimulation, blood pressure, and oxygen transportation in animals (e.g. horses, rats), but its use as a performance-enhancing drug in humans is not proven (Kuiper et al.,1998). By increasing the rate at which body fat is metabolized while increasing the body's basal metabolic rate (i.e thermogenic and lipolytic effects) Clenbuterol is used by body builders for ”cutting” off all the extra body fat that has been gained while on the bulking cycle (i.e. "cut period") (Kuiper et al.,1998). More recently it has become known for its off-label use for weight-loss and to increase lean mass despite the lack of any clinical evidence (Waldman and Terzic, 2012).

At altitude: No studies have been performed at altitude for AMS prevention or treatment.

Doping: Clenbuterol is included by WADA in the prohibited list of performance-enhancing drugs, banned *in*- and *out-competition* (WADA, 2016b).

Conclusion: Its use at altitude or in any aspect of mountaineering is not recommended.

Recommendations: In general, the use of inhaled β_2-agonists in non-asthmatic mountaineers is not recommended. Salmeterol at the dose of 125 μg twice per day could be used for HAPE prevention or treatment but only in conjunction with other medications. Recommendation Grade: 2B

4. β-BLOCKING AGENTS

Generic names inlcude: **ATENOLOL, ACEBUTOLOL, CARVEDILOL, LABETALOL, METOPROLOL, NEBIVOLOL, PINDOLOL, PROPANOLOL** β-blockers block the action of endogenous catecholamines such as epinephrine (adrenaline), and norepinephrine (noradrenaline), in particular on adrenergic ß-receptors, of the sympathetic nervous system (American_Pharmacists_Association 2012). Some agents block all β-adrenergic receptors (first-generation non-selective combined $\beta_1\beta_2$-blockers) while others are selective (second generation cardio β_1-selective agents) (Opie and Gersh 2009). Third-generation agents Nebivolol and Carvedilol also have added vasodilating properties (mediated by release of nitric oxide) or by adding α-adrenergic blockade as in Labetalol and Carvedilol, or acting via β_2-intrinsic sympathomimetic activity, as in Pindolol and Acebutolol (Opie and Gersh 2009).

β-blockers and sport: Bradycardia and the negative inotropic effects are of special importance when these drugs are used in sport since these changes decrease the myocardial oxygen demand (Tesch 1985). Exercise induced β-adrenergic stimulation leads to β-mediated coronary vasodilation. Thus, during exercise, the heart pumps faster and more forcefully, while the coronary flow is increased. Conversely, β-blockade should have a coronary vaso-constrictive effect with a rise in coronary vascular resistance. However, the longer diastolic filling time, resulting from the decreased heart rate in exercise, leads to better diastolic myocardial perfusion, to give an overall positive benefit (Tesch 1985). Bronchospasm occurs in susceptible individuals due to blockade of β_2-receptors, which mediate dilation in the bronchi. Asthma is a contraindication for β -blockers (American_Pharmacists_Association 2012). Peripheral vasoconstriction may result in cold hands and feet due to reduced cardiac output and possibly blockade of β_2-receptors, which promote vasodilation in blood vessels supplying skeletal muscles. Tiredness and fatigue may be due to reduced cardiac output exacerbated by blockade of β_2-receptors in skeletal muscle and associated with increased muscle activity (American_Pharmacists_Association 2012).

At altitude: The high prevalence of hypertension in the general population means that it is also common amongst skiers, hikers and visitors to moderate and high altitude. β-blockers are used for blood pressure regulation because they decrease sympathetic activity, but the frequency of therapeutic beta-blocker use in mountaineers is unknown (Bouissou et al.,1989; Dehnert and

Bartsch 2010; American_Pharmacists_Association 2012; Berg et al.,2004; Luks 2009; Tissot van Patot et al.,2005). As expected β-blockers limit the cardiac response to hypoxia but do not impair the ventilatory response and do not modify the susceptibility to high-altitude related illness (Richalet et al.,2013). Regular β-blocker intake in hypertensive elderly persons can provoke oxygen desaturation during submaximal exercise leading to reduced exercise tolerance in people taking β-blockers at acute high altitude (Faulhaber et al.,2003). In a study performed to evaluate the effects of different β-blockers (selective and non-selective) on cardiopulmonary response to exercise at high altitude, Valentini and Coll (Valentini et al.,2012) found that Nebivolol may be preferred due to better preserved peak oxygen consumption (VO_2), increased peak minute ventilation (VE) and peripheral vasodilation. β-blockers may induce bronchospasm in susceptible individuals with “exercise and cold air induced asthma” (Van Wijck et al.,2012). β-blockers may interfere with thermoregulation in response to heat or cold (Mieske et al.,2010). β-blockers are contraindicated in individuals with Raynaud’s phenomenon (American_Pharmacists_Association 2012). Frostbite may be a risk at high altitude (Luks 2009).

Doping: β-blockers are prohibited *in-competition* in specific sports. In archery and shooting they are also prohibited *out-competition.* Currently β-blockers are accepted for competition climbing (WADA 2016b).

Generic name: **IVABRADINE**

Ivabradine is a cardiotonic agent, approved by the European Medicines Agency in 2005 (American_Pharmacists_Association 2012). It is a pure heart rate-lowering agent, with no negative inotropic effect or blood pressure reduction, as with β-blockers, nor any rebound on cessation of therapy (DiFrancesco 2004). Ivabradine provides an effective and significant dose-dependent reduction in heart rate, which is also reflected in a reduction in the rate pressure product leading to a reduction in myocardial oxygen consumption (Yusuf and Camm 2003). So far no studies at altitude exist.

Conclusions: β-blockers may be helpful for blood pressure regulation at high altitude because of increased sympathetic activity, but they reduce the maximum pulse rate and therefore limit maximal workload in healthy subjects, and can decrease the circulation to the extremities, potentially putting the person at a higher risk of frostbite. Patients with coronary heart disease may benefit by the use of β-blockers because the work of their myocardium will be optimized and the oxygen demand lowered. β-blockers have been used to reduce the physical symptoms of stress and anxiety and consequently might be considered by sport climbers.

Recommendations: The use of β-blockers may be recommended for patients who are already established on chronic anti-hypertensive β-blocker medication. The use of beta-blockers at high altitude limits the cardiac response to hypoxia, does not impair the respiratory response and does not modify the susceptibility to high altitude related illnesses. Recommendation Grade: 1B

5. DIURETICS

At altitude: Dehydration due to exertion, low humidity, vomiting or diarrhoea may be exaggerated in those taking diuretics. Electrolyte disturbances, particularly hypokalaemia, can develop and predispose subjects to life threatening consequences. Rehydration salts and dried fruit (especially apricots and bananas) may resolve the problem (West et al.,2012).

Doping: According the WADA Prohibited List, diuretics belong to the group of masking agents. Drugs in this category are prohibited at *all times* (WADA 2016b).

Generic Name: **ACETAZOLAMIDE**

Acetazolamide is a carbonic anhydrase inhibitor and its predominant site of action is the luminal membrane of the proximal convoluted renal tubule where it catalyzes the dehydration of H_2CO_3.

By blocking carbonic anhydrase, inhibitors block $NaHCO_3$ reabsorption causing diuresis, signi-fycant HCO_3^- losses and hyperchloraemic metabolic acidosis, resulting in better arterial oxygenation. More recently it has been speculated that carbonic anhydrase inhibitors may act on the brain and the lungs as well, reducing aquaporin-mediated transmembrane water transport, and with anti-oxidant actions, vasodilation and anti-inflammatory effects (Swenson, 2016), Drowsiness, dizziness, fatigue, headache, malaise, taste alteration (it makes fizzy drinks taste flat) and paraesthesia are common side effects. Acetazolamide may enhance the hypotensive effect of other antihypertensive drugs (Katzung et al.,2012; Waldman and Terzic 2012). Acetazolamide (250 mg) mitigates an acute hypoxia induced rise in cerebral blood flow, it reduces an elevated cerebral aerobic metabolism, thereby improving cerebral tissue oxygenation (Swenson, 2016; Wang et al., 2015).

At altitude:

Prevention of AMS and HACE: Acetazolamide is commonly used in individuals with a history of acute mountain sickness (AMS) or when a graded ascent and acclimatization is not possible (e.g. when rapid ascent is necessary for rescue purposes or when flight into a high-altitude location). Acetazolamide minimises the symptoms of AMS as one acclimatises but it does not mask the symptoms of altitude illness (Ritchie et al.,2012). Acetazolamide (125–250 mg twice a day) should be started either the day before (preferred) or on the day of ascent and may be discontinued after staying at the same elevation for 2-3 days (i.e. after acclimatization is achieved) or when the highest elevation is reached and descent initiated (Aldashev et al.,2005; Beaumont et al.,2007). Higher doses are not usually required (Basnyat et al., 2006; Basnyat et al., 2003; Carlsten et al.,2004; Hackett and Roach, 2001; van Patot et al.,2008). For children the dosage is 2.3 mg/kg every 12 hours. In a systematic review, Kayser concluded that the degree of efficacy of acetazolamide for the prevention of AMS is limited when the baseline risk is low, and there is some evidence of dose-responsiveness, the risk of paraesthesia is increased with all doses and the risk of polyuria and taste disturbance is increased at 500 and 750 mg/day (Kayser et al.,2012). When a rapid ascent is unavoidable use of Acetazolamide to aid acclimatization might be warranted. People with known previous susceptibility to AMS may benefit from prophylaxis to aid in acclimatization. Side effects do occur with Acetazolamide, such as paraesthesia, skin rashes, dyspepsia, lassitude, fatigue and possible dehydration in 30-40% of subjects but generally are well tolerated. The most important risks are severe acidosis, respiratory failure and encephalopathy in subjects with renal, pulmonary and hepatic diseases (Swenson et al., 2014). Some authorities recommend trial doses at sea level prior to a high altitude trip.

Sulfa allergy is generally considered a contraindication to Acetazolamide use (Pollard et al.,2001, Hackett and Roach, 2001). Acetazolamide is a non-antibiotic sulphonamide and many allergies are caused by sulphonamide antibiotics. The absence of cross-reactivity between sulphonamide antibiotics and sulphonamide non-antibiotics (Strom et al.,2003), individuals with a history of allergy do not necessarily have to avoid the use of Acetazolamide (Kelly and Hackett, 2010)

<u>Treatment of AMS:</u> Acetazolamide is used as a treatment for mild AMS (Goldstein et al.,2010) and combined with Dexamethasone for severe AMS (Luks et al.,2014) where, combined with supplemental oxygen and a portable hyperbaric chamber it can buy time for the vital descent. The dose recommended is 250 mg twice daily (Luks et al.,2014). There are no studies of treatment of acute altitude illness in children with Acetazolamide (Pollard et al.,2001).

<u>Prevention of HAPE</u>: Acetazolamide decreases pH in fluid compartments and has been shown to blunt hypoxic pulmonary vasoconstriction. As a result, Acetazolamide reduces pulmonary artery systolic pressure, ventilation increases and oxygenation improves (Grissom et al.,1992; Jonk et al.,2007, Ke et al. 2013). Research studies in animals (Hohne et al.,2004, Shimoda et al., 2007), and in humans (Teppema et al.,2007, Ke et al. 2013) showed that this mechanism may play a role preventing HAPE, while another study could not draw any conclusions about its efficacy in preventing HAPE (Basnyat et al.,2008b). Acetazolamide seems to be a rational choice for HAPE prevention supported by clinical experience, but definitive data are lacking (Luks et al.,2014).

A randomised, double-blind, placebo-controlled study was conducted to evaluate the effects of Theophylline and Acetazolamide in the treatment of sleep-disordered breathing (SDB) after fast ascent to high altitude (3454 m) and the authors concluded that both oral slow release drugs are effective (Fischer et al.2004). Medical research on Acetazolamide has only been undertaken to an altitude of 6300 m (Hackett et al.,1985). It is not proven whether any benefit is conferred at higher altitude. Acetazolamide is now licensed for high altitude use by US FDA (American_Pharmacists_Association, 2012), but since its use is still “off licence” in many other countries some doctors are reluctant to prescribe it. In many countries Acetazolamide is freely available without a prescription.

At altitude, Acetazolamide seems to affect performance by at least two mechanisms: i) “feeling better” with less symptoms of AMS, and ii) a direct increase of the hypoxic ventilatory response by the induced metabolic acidosis thereby increasing O_2 uptake (Leaf and Goldfarb, 2007). Fulco showed that endurance performance was impaired with Acetazolamide only at sea level but not at altitude, probably due to off-setting secondary effects resulting from acidosis, which resulted in an increased oxygen pressure gradient from capillary to exercising muscle (Fulco et al.,2006). On the contrary, Garske reported that Acetazolamide reduces exercise capacity and increases leg fatigue under hypoxic conditions (Garske et al.,2003). McLellan reported a decrease of exercise performance of only 37% with Acetazolamide vs. 45% in the placebo group (McLellan et al.,1988). More recently Bradwell et al. assessed the effect of Acetazolamide on exercise performance evaluated by bicycle ergometer during early acclimatization followed by rapid ascent to 3459 m in twenty healthy subjects (placebo or Acetazolamide 250 mg twice daily). In a study assessing the effects of Acetazolamide on exercise at altitude, performance was reduced in subjects on Acetazolamide in terms of perceived difficulty and the failure to complete the test ($p<0,01$) and SpO_2 decreased more during exercise ($p<0.005$), particularly in older subjects, despite a higher resting SpO_2 ($p<0.001$) and fewer AMS symptoms before the test (Bradwell et al.,2014).

Doping: Acetazolamide is listed by WADA because it can camouflage doping tests but not because it has any effect on performance (WADA, 2016b).

Conclusions: Acetazolamide is currently the gold standard if drugs must be used for the prevention of AMS and probably HACE (Severinghaus, 2001, Luks et al.,2014). Acetazolamide does not protect against worsening AMS with continued ascent (Luks et al.,2014).

Recommendations:

AMS-HACE prevention: Gradual ascent with natural acclimatisation must be the gold standard for any high altitude venture but if drug use is required for a specific clinical reason then Acetazolamide (125 mg twice daily) should be started either the day before (preferred) or on the day of ascent and may be discontinued after staying at the same elevation for 2-3 days (i.e. after acclimatization is achieved), or when the highest elevation is reached and descent initiated. Recommendation Grade: 1A

AMS treatment: Acetazolamide (250 mg twice daily) alone for mild AMS, or in severe AMS combined with Dexamethasone, supplemental oxygen, a portable hyperbaric chamber and descent is recommended. Recommendation grade: 1B.

HAPE prevention: Acetazolamide may be useful for HAPE prevention. Recommendation Grade: 2C.

6. ERYTHROPOIETIN

Erythropoietin, also known as EPO**,** haematopoietin or haemopoietin, is a glycoprotein hormone that controls erythropoiesis. While liver production predominates in the foetal and perinatal period, renal production is predominant during adulthood. Exogenous erythropoietin is produced by recombinant DNA technology in cell culture. Several different pharmaceutical agents are available with a variety of glycosylation patterns (epoetin, darbepoetin) and are collectively called erythropoiesis-stimulating agents (ESAs) (American_Pharmacists_Association, 2012; Jelkmann, 2007).

US Boxed Warning: ESAs increase the risk of serious cardiovascular events, stroke, thromboembolic events, mortality and tumour progression when administered to target haemoglobin levels > 12 g/dL (American_Pharmacists_Association, 2012).

At altitude: Drugs as EPO, ESAs or other erythropoietic products aim to stimulate erythropoiesis at altitude. It should be stressed that all low oxygen states, including hypoxia of high altitude, cause "physiological" EPO release. By increasing oxygen-carrying capacity EPO increases aerobic capacity and performance in endurance sports, including mountaineering but at higher risk of thrombosis due to dehydration (Tabin and McIntosh, 2001). Other studies using simulated altitude conditions and oxygen deprivation (e.g. acute exposure to 12.6% O_2) have shown that ESA treatment causes haemoglobin and accordingly arterial oxygen content to increase both in normoxia and hypoxia, but at maximal exercise in hypoxia, maximal oxygen uptake (VO_2max) is not increased (Lundby and Damsgaard, 2006). Prolonged administration of recombinant human erythropoietin increases submaximal performance more than maximal aerobic capacity (Thomsen and others 2007). A study performed at Annapurna base camp (4,130 m) (Heo et al.,2014) showed that epoetin α pretreatment decreased AMS incidence and those requiring immediate descent with no adverse effects. The fact that EPO or ESAs have contradictory effects on performance illustrates that their use is based on theory rather than medical evidence. This increase of red blood cells and thickening of the blood comes with the risk of serious cardiovascular events, stroke and other thromboembolic events. High altitude exposure initially causes rapid plasma and extracellular volume losses while erythrocyte volume is unaffected thus viscosity increases. Diluting the blood to reduce viscosity with a plasma volume expander administrated simultaneously with EPO will probably increase exercise capabilities more than augmenting the total red cell volume alone (Sawka et al.,2000). In reality this increased viscosity of the blood results in reduced cardiac output and in less oxygen carrying capacity in the blood (Young et al.,1996).

<u>Doping</u>: Blood doping is defined as the use of illicit erythropoietic products (EPO, ESAs, peginesatide, hypoxia-inducible factor [HIF] stabilizers) and increasing aerobic capacity methods (blood transfusions, blood substitutes as haemoglobin-based oxygen carriers [HBOCs] and per-fluorocarbons [PFCs]), used to maximize the uptake of O_2 and to enhance the O_2 transport to the muscles thus improving athlete's aerobic capacity (VO_2 max) and endurance (Robach et al.,2008). According the WADA Prohibited List, all these products and methods are prohibited at *all times* (WADA, 2016b).

<u>Conclusions</u>: EPO and ESAs aim to increase erythropoiesis and by this VO_2max resulting in little improvement in athletic performance. The side effects may be very dangerous at high altitude. Combining the unpredictable effects of EPO on each climber's individual physiology associated with the possibility of dehydration, malnourishment and altitude sickness, all possible events when living at high altitude, makes EPO use risky for mountaineers.

<u>Recommendations</u>: Avoid use of EPO. It is better to rely on sophisticated changes in the blood, with natural acclimatisation that have evolved over millions of years. Recommendation Grade: 1C.

7. GLUCOCORTICOSTEROIDS

Glucocorticosteroids (glucocorticoids) are a class of steroid hormones present in almost every vertebrate animal cell.

Generic name: **DEXAMETHASONE**

Dexamethasone is a synthetic steroid medication (Blue and Lombardo, 1999) with a variety of therapeutic actions. It suppresses inflammation by stimulating neutrophil migration, reversing capillary permeability and decreasing production of inflammatory mediators, and it acts as an immunosuppressant agent. It may be used in management of cerebral oedema associated with brain tumor. Unlicensed use includes: prevention and treatment of AMS and HACE (American_Pharmacists_Association, 2012; Ferrazzini et al.,1987). Corticosteroids represent one of the most important drug classes for prevention and treatment of AMS, and their benefits include their anti-inflammatory and anti-edema effects. More recently it has been speculated that corticosteroids may protect against increase in vascular endothelial and blood-brain barrier permeability, suppress inflammatory cytokines, reduce ROS formation up-regulating endogenous anti-oxidant enzymes synthesis and with a potent sympatholytic action for suppression of adrenergic tone (Swenson, 2016)

Patients receiving Dexamethasone report moderate–severe problems with insomnia (45%), indigestion and epigastric discomfort (27%), agitation (27%), increased appetite (19%), weight gain (16%) and acne (15%). Side effects encompassing cardio-circulatory function, lungs, gastrointestinal system, skin and hair are also reported (American_Pharmacists_Association, 2012).

At least 853 drugs are known to interact with Dexamethasone. For instance, if combined with Acetylsalicylic acid, it increases its antiplatelet effects increasing the risk of internal bleeding from stomach and gut, brain, retina and respiratory system. Dexamethasone should be taken with meals to decrease gastrointestinal upset. Salt in the diet should be reduced to avoid fluid retention. Ethanol or Acetylsalicylic acid, which may enhance gastric mucosal irritation should be avoided (American_Pharmacists_Association, 2012).

At altitude: Medical efficacy for the prevention and treatment of high-altitude illness. Dexamethasone is effective in reducing the incidence of AMS during rapid ascent (Dumont et al.,2000; O'Hara et al.,2014). Possible mechanisms include improvement in microcirculatory integrity, and reduction in cerebral blood flow by vasoconstriction. It has also the ability to stimulate sodium and water reabsorbtion while also increasing the release of nitric oxide with overall pulmonary vasodilation (Maggiorini et al.,2006). Comparing Dexamethasone with Acetazolamide or placebo, the use of Dexamethasone significantly reduced the incidence of AMS and the severity of symptoms, without affecting physical or mental aspects ($p<0.05$) (Ellsworth et al.,1987; Ellsworth et al.,1991). A study showed a decrease of cognitive deficits in asymptomatc subjects caused by subclinical cerebral oedema (Lafleur et al.,2003).

Dexamethasone is effective in the **prevention** of AMS and HACE (2 mg every 6h or 4 mg every 12 h) and HAPE in *susceptible* individuals (4 mg every 6 h). The duration of use should not exceed an absolute maximum of 10 days with gradual dose reduction to minimise serious side effects (Dunin-Bell and Boyle, 2009; Luks, 2009; Subedi et al.,2010; Tang et al.2014). Dexamethasone does not facilitate physiological acclimatization so individuals using this drug prophylactically are not physiologically protected against the hypoxic environment. If it is suddenly stopped at altitude expect a rebound effect with rapid onset of altitude-related symptoms. If used as a prophylactic drug for AMS it may eventually trigger symptoms mimicking AMS (e.g. sleep disorders, fatigue, mania, oedema, muscle weakness) (Subedi et al,. 2010). Some authorities consider Dexamethasone a second option for AMS prevention in cases of Acetazolamide intolerance (West et al.,2012).

Dexamethasone is very effective in the **treatment** of severe AMS (4 mg every 6 h) and is the first-line drug for HACE treatment (8 mg once then 4 mg every 6 h (Levine et al.,1989; Luks et al., 2014). If Dexamethasone is used for treatment it should only be done to buy time for the essential descent or when descent is impossible (Schoene 2005).

Rumour has circulated that inhaled steroids may prevent AMS. Two recent double-blind, randomized controlled trials demonstrated the efficacy of inhaled Budesonide for the prevention of AMS (Chen et al.,2015; Zheng et al.,2014), but clinical experience with this medication at high altitude is very limited. No other inhaled steroids have been tested at high altitude.

<u>Ability to maintain physical performance at high altitude.</u> Many studies suggest that Dexamethasone may be useful in improving physical performance increasing maximal aerobic capacity and oxygen uptake kinetics, reducing pulmonary arterial resistance, increasing alveolar fluid clearance and also improving cognitive ability (Fischler et al.,2009; Peacock 1998; Siebenmann et al., 2011). Deaths have occurred when Dexamethasone is taken as an aid to going higher faster.

Overconfidence in the drug's properties can lead to poor risk assessment when planning high-altitude climbs (Subedi et al.,2010).

Doping: The WADA prohibits all glucocorticosteroids used *in-competition* whether administered by oral, intravenous, intramuscular or rectal routes (WADA 2016b). Athletes who are prescribed glucocorticoids may take these medications *out-competition* without submitting a therapeutic use exemption (TUE) as long as the prohibited substance has cleared their system prior the time defined as *in-competition*. If athletes need to use these drugs shortly before or during competition, they must obtain a TUE. Inhalation of glucocorticoids (e.g. for asthma) is permitted. Injections of glucocorticoids around tendons, into joints and epidural (into the spine) are permitted, but an injection into a muscle in prohibited.

Conclusions: The use of corticosteroids has to be a personal decision for mountaineers. These agents can cause significant side effects and the risk/benefit equation is very different from that for Acetazolamide (Basnyat 2002). Dexamethasone should be available on any high altitude expedition for treatment of HACE and HAPE to buy time for rapid descent or when the descent is impossible (Levine et al.,1989; O'Hara et al.,2014). It can be lifesaving and use in short courses for emergency treatment will avoid many of the potential long-term side effects.

Recommendations:

AMS prevention: Gradual ascent with natural acclimatisation must be the gold standard for any high altitude venture but if drug use is required for a specific clinical reason and Acetazolamide is contraindicated Dexamethasone can be considered for prevention of AMS and HACE (2 mg every 6 h or 4 mg every 12 h). Recommendation Grade: 1B.

Dexamethasone can be used in preventing HAPE in susceptible individuals (4 mg every 6 h). Recommendation Grade: 1B

AMS treatment: Dexamethasone can be used in the treatment of severe AMS (4 mg every 6 h), and is the first-line drug for HACE (8 mg once then 4 mg every 6 h). Recommendation Grade: 1B. Inhaled Budesonide seems to be effective in the prevention of AMS. Recommendation Grade: 1B

Dexamethasone should be available on any high altitude expedition for treatment of HACE and HAPE to buy time for rapid descent (Recommendation Grade: 2B).

8. OXYGEN

Oxygen is widely available and commonly prescribed by medical and paramedical staff. When administered correctly it may be life-saving, but oxygen is often given without careful evaluation of its potential side effects. Like any drug there are clear indications for treatment with oxygen and appropriate methods of delivery. Inappropriate dose and failure to monitor treatment can have serious consequences (Bateman and Leach, 1998).

Oxygen at high altitude: Although the percentage of oxygen in inspired air is constant at different altitudes, the fall in atmospheric pressure with ascent decreases the partial pressure of inspired oxygen and hence the driving pressure for gas exchange in the lungs. The weight of air above us is responsible for the atmospheric pressure, which is about 760 mmHg (101 kPa) at sea level and, as oxygen is 20.9% of dry air, the inspired oxygen pressure is 149.6 mmHg (20 kPa) (Peacock, 1998). Atmospheric pressure and inspired oxygen pressure fall with altitude to be 50% of the sea level value at 5500 m and only 30% of the sea level value at 8848 m (summit of Mt. Everest) (Peacock, 1998). The first line of O_2 transport from the environment to the blood is the ventilatory air convection. West has pointed out that this function is the most important adaptive parameter during ascent to high altitude and that it allows some acclimatised humans to reach the top of Mt. Everest (West, 1982; 1990b). Hyperventilation is one of the most important features of acclimatization to high altitude. Resting ventilation at extreme altitudes increases up to fourfold and exercise ventilation for a given work level increases to the same extent. Hypoxic stimulation of the peripheral chemoreceptors is the chief mechanism for the hyperventilation but there is also evidence that central sensitization of the respiratory centres occurs. Cardiac output increases in responses to acute hypoxia but returns to normal in acclimatized lowlanders. Oxygen uptake at extreme altitudes is markedly limited by the diffusion properties of the blood gas barrier. As a consequence the maximal oxygen consumption of a climber near the summit of Mt. Everest is near his basal oxygen requirements. Maximal oxygen consumption is so sensitive to barometric pressure that it may be that seasonal or day-to-day variations will affect the chances of a climber reaching the summit without supplementary oxygen (West,1999; West et al.,2012).

Oxygen transport by red blood cells is regulated by erythropoiesis and Hb-O_2-affinity. The O_2 carrying capacity is characterized by changes in haematocrit, red blood count or the mass of circulating red blood cells. Erythropoiesis is controlled by the hormone erythropoietin, which induces slow changes of the O_2-transport capacity. The Hb-O_2-affinity is modified mainly by pH, and 2,3-DPG. In hypoxia at high altitude, despite their apparently diverse effects, a compromise seems to be adopted optimizing both arterial O_2-loading and peripheral O_2-unloading. In contrast to erythropoiesis, adjustments of the Hb-O_2-affinity occur quickly and allow rapid adjustments of O_2-binding and release. In severe hypoxia adjustments of both, haematocrit and Hb-O_2-affinity, are insufficient to maintain tissue O_2-supply (Lenfant et al.,1968; Mairbaurl, 1994).

Delivery systems: Providing supplemental oxygen in adverse conditions at 8000 m is not simple. Frozen valves, deformed masks, ice formation in the tubing and other problems can prevent the delivery of the right amount of oxygen at the right time. Too much and there is waste of gas, too little and the climber may die. Modern light, reliable systems are now available (Windsor et al.,2005; Windsor et al.,2008).

Supplemental Oxygen and Mountaineering

Ethics: The ethics of oxygen use have been extensively debated since the 1920s and will continue to be debated for many years to come (UIAA Tyrol Declaration, 2002). There is no doubt that oxygen is a drug, in many countries available only on prescription and that it improves exercise tolerance at altitude. Depending on the oxygen flow 8000 m peaks will be physiologically “reduced” to 6500 to 7400 m summits (Küpper et al., 2010). Some say that any drug or artificial aid, which increases performance, is not acceptable, and every mountaineer will express respect for the very few climbers who have summited 8000 m peaks without using supplementary oxygen. Most people can acclimatise to 5000 m so they can climb peaks of over 6000 m from a high camp. It is only well above 7000 m where the oxygen debate is relevant.

Medics: Reaching the summit of 8000 m peaks is dangerous, and many mountaineers are unaware of the dangers of hypoxia at extreme altitude when they overcome the unpleasantness of acclimatisation at lower altitude (4000-5000 m). Few individuals have the physiological and mental capacity to reach extreme altitudes (>8000 m) and return safely without using supplemental oxygen. There is no doubt that the use of oxygen at extreme altitude reduces the risks of death**,** especially during descent when mountaineers are often near exhaustion and vulnerable to accident, poor decision making, storm or illness (Pollard and Clarke 1988).

Supplementary oxygen provides the human body with the one substance it really lacks at extreme altitude. Oxygen does not affect performance at sea level, because neither the amount of available oxygen nor its partial pressure is the limiting factor for maximal performance. This changes dramatically at extreme altitude, where the oxygen cascade from the atmosphere to the mitochondria is limited by decreased inspiratory PO_2 and capillary-mitochondrial ΔPO_2 (West 1990a). Supplemental oxygen improves exercise tolerance (West 1993), allows a significant improvement in maximal steady state power output (Morris et al.,2000), benefits climbers subjectively and improves SaO_2 in the resting state and during exercise (Grocott et al.,2009; Huey and Eguskitza 2000a; West 1995; Windsor et al.,2007). Climbers who reach extreme altitudes without using supplemental oxygen may have more effective respiratory acclimatization than others and have therefore a higher PaO_2 when breathing ambient air. If supplemental oxygen is withdrawn in the hypoxic environment (Grocott et al.,2009) there is a high risk from the sudden onset of HACE and HAPE (Pollard and Clarke, 1988). Supplemental oxygen enhances climbing speed and performance (Huey and Eguskitza, 2000a) thereby decreasing time spent at extreme altitude and reducing physical deterioration (Huey and Eguskitza, 2001; Pollard and Clarke 1988). It reduces cognitive impairment, but also lures less experienced climbers onto extreme objectives (Huey and Eguskitza, 2000b; Pollard and Clarke 1988).

Significant improvements are expected when using oxygen at extreme altitude. Few studies have attempted to analyse factors that influence death rate, but data about risk and mortality while using oxygen or not are scant and difficult to analyse in this extreme environment. Limited data are given for the most popular peaks and the cause of death is analysed by different categories: peak altitude, geographical region, climbing season, age, gender and experience. Ascents are also analyzed by team composition, member and hired personnel, and if commercial or non-commercial expeditions. These populations are difficult to compare as those not using supplementary oxygen are often more experienced, fitter and climb in a lighter style on more technically difficult ground. The risk of death during ascent and descent from the summit of Mt. Everest or K2 is increased for climbers without supplemental oxygen: 8.3% vs. 3.0% on Mt. Everest, 18.8% vs. 0% on K2 (Huey and Eguskitza, 2000a; Huey and Eguskitza, 2000b; Huey et al.,2001). These raw data do not indicate the primary cause or death or contributing factors. According to Himalayan Database, differences in death rates only reached statistical significance on Mt. Everest (Salisbury and Hawley, 2011).

Across all altitudes, lethal falls during descent are three times higher than during ascent and hypoxia can contribute to accidents via disorientation, misjudgments or exhaustion (Salisbury and Hawley, 2011). Another study shows that, while 70% of deaths at altitude over 6500 m reflect the hazardous mountain terrain (e.g. crevasse, avalanches, storm), altitude hypoxia contributes to the 30% of deaths ascribed to HACE, HAPE or neurological damage impairing motor and cognitive activities. Supplemental oxygen could reduce these “medical” deaths (Pollard and Clarke, 1988).

The brains of mountaineers operating at extreme altitude demonstrate significant long-term deficit involving motor- (Di Paola et al.,2008; West, 1990b) and cognitive activities (e.g. impaired concentration, short-term memory, and ability to shift concepts and control errors) (Firth et al.,2008; Grocott et al.,2009; Hornbein et al.,1989; Richalet et al., 1999; Turner et al.,2015; Virues-Ortega et al.,2004; Yan, 2014), sometimes persisting after return to sea level (West 1990b) with structural neurologic damage (e.g. frontal subcortical lesions, cortical atrophy) (Garrido et al.,1993; Garrido et al.,1995). Amateur climbers are at higher risk than professionals (Fayed et al.,2006). Repeated extreme-altitude exposure can cause mild but persistent cognitive impairment (Regard et al.,1989), while one paper shows no significant deficit in acclimatised individuals climbing to 7500 m (Merz et al.,2013). Death due to acute hypoxia during ascent or descent following failure of supplemental oxygen circuits are not unusual (e.g. 2 deaths out of 62 during 1978 to 2006 on Mt. Everest) (Firth et al.,2008)

Recent improvements in open-circuit systems for mountaineers have reduced weight whilst increasing comfort and reliability (Windsor et al.,2008; Windsor et al.,2005). Room oxygen enrichment (e.g. to 24%) may improve sleep and subsequent day-time performance at high altitude (Barash et al.,2001; Luks et al.,1998; West 2016).

Doping: No formal competitions take place at extreme altitude so WADA has made no judgment on oxygen use.

Conclusions: It is for the individual climber to make their own ethical and tactical decisions. Supplemental oxygen should be available on climbing expeditions to 8000 m peaks for optimal treatment of HACE and HAPE. Supplemental oxygen is recommended for rescues at high altitude (> 6500 m). Medically UIAA Medcom recommends the use of supplementary oxygen on peaks above 7500 m. Being active mountaineers, the UIAA Medcom members do admire those mountaineers with the experience, skill, fitness and physiology to climb safely above this altitude without supplementary oxygen whilst being aware of the risks involved.

Recommendations:

Supplemental oxygen should be available on climbing expeditions to 8000 m peaks for optimal treatment of HACE and HAPE. Recommendation Grade: 1A

Supplemental oxygen should be provided in rescues at high altitude (> 6000 m). Recommendation Grade: 1A.

9. SLEEP MEDICATION

Sleeping difficulty is very common with acute high altitude exposure and can prove very uncomfortable and impair daytime activities. Sleep disturbances were reported by more than 70% of participants in AMS treatment trials (Ainslie and others 2013). These complaints are associated with frequent brief arousals. The main concern when considering the use of sleep medications (hypnotics) at high altitude is whether the sleep disruption is an environmental effect or a physiological one related to poor acclimatization or an over-active respiratory response to high altitude leading to periodic breathing (Tseng et al.,2015; Kupper et al.,2008a). Up to 3500 m periodic breathing may be of advantage because it stabilizes oxygen saturation at a relatively high level, but at higher altitudes disadvantages predominate and frequent arousals cause total sleep deprivation and exhaustion (Zielinski et al.,2000). Recent research has shown that direct hypoxia has a far greater effect upon sleep at altitude than previously thought (Eichenberger et al.,1996; Windsor et al., 2012). If the individual is well acclimatized with no other signs or symptoms of AMS, it is not unreasonable to consider sleep medications to prevent the dangers of sleep deprivation (Taylor et al., 2016). Sleep medication, not hitherto included in the 2016 WADA list, used in conjunction with energy drinks and alcohol may result in an intoxication, similarly to the effects of some recreationally abused drugs, which are WADA prohibited (Taylor et al.,2016).

9.1 THEOPHYLLINE – ACETAZOLAMIDE (see also respective chapters)

Insomnia at altitude is associated with increased waking and periodic breathing or apnea due to effect of hypoxemia and poor acclimatization. Acetazolamide has been shown to have beneficial effects on sleep disturbances (Richalet 2013; Rodway et al.,2011; Wickramasinghe and Anholm, 1999; Windsor and Rodway, 2012). A randomised, double-blind, placebo-controlled study was conducted to evaluate the effects of both Theophylline and Acetazolamide in the treatment of sleep-disordered breathing after fast ascent to high altitude (3454 m), showing that both drugs are effective in normalising high-altitude sleep disorders. Both Theophylline (250 mg x 2 daily) and Acetazolamide (250 mg x 2 daily) reduced oxyhemoglobin desaturation during sleep, with a reduction in obstructive events during sleep compared with the incidence of central apnoea of controls (Kupper et al.,2008b). Acetazolamide also significantly improved basal oxyhemoglobin saturation during sleep compared with Theophylline (86.2% versus 81%) (Fischer et al.,2004). In addition to the established side effects of Acetazolamide, if taken at night its diuretic effect can interrupt sleep.

Recommendations: Theophylline and Acetazolamide should be considered for reducing the occurrence and intensity of sleeping disorders. Recommendation Grade: 1B

9.2 HYPNOTICS

Insufficient data exist to determine which agent is most effective at altitude, nor is it known, whether combination therapy with Acetazolamide and a hypnotic agent offers any benefits over monotherapy (Luks 2008).

9.2.1 BENZODIAZEPINES

Hypnotic benzodiazepine side effects are related to central nervous system depression, including somnolence, dizziness, fatigue, ataxia, headache, lethargy, impairment of memory and learning, longer reaction time and impairment of motor functions (including coordination problems), slurred speech, decreased physical performance, numbed emotions, reduced alertness, muscle weakness, blurred vision (in higher doses), and inattention (American_Pharmacists_Association 2012; Katzung et al.,2012). All are potentially dangerous in the event of a standard 3 am alpine start.

Generic name: L**OPRAZOLAM**

Some studies demonstrated that benzodiazepines improve sleep quality and do not aggravate periodic breathing (Duff and Gormly 2012; Richalet 2013). Goldenberg showed that Loprazolam (1 mg) did not worsen either "slow-wave sleep" (SWS) depression or apneas and allowed normal sleep reappearance after acclimatization (Goldenberg et al.,1988; Goldenberg et al.,1992)**.** On the contrary**,** other limited evidence suggests it may cause hypoventilation at high altitude (Roggla et al.,1994). Benzodiazepines with a long half-life such as diazepam risk causing accumulative impairment of reasoning.

Benzodiazepine use in this environment should be discouraged especially when combined with alcohol.

Generic name: **TEMAZEPAM**

Temazepam, a short-acting benzodiazepine, has been shown to improve sleep quality but to only cause a small decrease in mean oxygenation in un-acclimatized climbers (Dubowitz, 1998).

The addition of Theophylline or Aminophylline has been shown to reduce the sedative effects of Temazepam and other benzodiazepines (Katzunget al.,2012) .

At altitude: During a Himalayan expedition both Acetazolamide (250 mg x 2) and Temazepam (10 mg) were used between 4100 and 4846 m. Compared with placebo (only Acetazolamide 250 mg x 2), there were no prolonged sleep latencies, less wakefulness and drowsy sleep, increased sleep duration in the first 6 hours after ingestion (290 and 231 minutes respectively) and sleep quality evaluated by visual analog scale (VAS) was at sea level values (Nicholson et al.,1987).

In a randomized, blinded, cross-over, placebo controlled trial at base camp of Mt. Everest (5300 m), participants taking Temazepam (10 mg) showed no significant drop in mean oxygen saturation during sleep. The quality of sleep improved as a result of a reduction in the number of awakenings, a greater respiratory stability and fewer episodes of periodic breathings (Dubowitz 1998). In another double-blind, randomized, cross-over trial at 5000 m Temazepam (10 mg) was effective in reducing periodic breathing, safe to use and without any adverse effect on next-day performance (Nickol et al.,2006).

Short-acting benzodiazepine Temazepam (10 mg) given with Acetazolamide (500 mg slow-release) improved sleep and maintained SaO_2%, counteracting a 20% decrease in SaO_2% when Temazepam was given alone (Manang, Nepal, at 3540 m) (Bledsoe et al.,2009).

Lastly, the first comparative randomized, double-blind trial of Temazepam (7.5 mg) vs. Acetazolamide (125 mg) taken at bedtime for one night at an altitude of 3540 m showed no difference with regards to mean nocturnal oxygen saturation, proportion of the night spent in periodic breathing, relative desaturations, sleep onset latency, awakenings, wake after sleep onset, sleep efficiency, daytime drowsiness or change in self-reported Lake Louise Score. The Acetazolamide group reported significantly more awakenings to urinate (Tanner et al.,2013).

Conclusions: Benzodiazepines are controversial. As a general rule the use of drugs such as Diazepam should be discouraged as they decrease the respiratory drive causing hypoventilation, especially if combined with alcohol. Studies would suggest that Temazepam may have a useful role in management of altitude insomnia.

Recommendations: Benzodiazepines should not be used at high altitude. Alcohol will increase benzodiazepines related adverse effects, e.g. nocturnal hypoventilation and desaturation and day sedation. Recommendation Grade: 2B.

Between 4000 and 5000 m co-ingestion of Acetazolamide (500 mg) and Temazepam (10 mg) may result in a sleep quality comparable to sea level values. Recommendation Grade: 1B.

Temazepam (10 mg) taken up to 5300 m may improve sleep quality by reducing awakening, and providing a greater respiratory stability and fewer episodes of periodic breathings, without any negative side effects during night or detrimental effects on next day's performance. Recommendation Grade: 1A.

9.2.2 NON BENZODIAZEPINES

Generic names: **ZOLPIDEM**, **ZALEPLON**

The new generation hypnotic drugs, Zolpidem and Zaleplon, are at least as efficacious as benzodiazepines and may offer advantages in terms of safety due to their very short half-life. Frequency of side effects may be dosage and age dependent, and include headache, somnolence, dizziness, hypertension, rash and urticaria, arthralgia (American_Pharmacists_Association, 2012; Muller et al.,1987).

At altitude: Zolpidem improved sleep characteristics at 4000 m, inducing a decrease in sleep onset latency (placebo, 22 +/- 12 min versus Zolpidem, 10 +/- 6 min), an increase in SWS (stage three of non-REM sleep) duration (placebo, 46 +/- 28 min versus Zolpidem, 69 +/- 28 min), and a reduction in the arousal index during SWS (placebo, 7.4 +/- 4.1 per h versus Zolpidem: 2.4 +/- 1.0 per h) (Beaumont et al.,1996) .

A 2007 double-blind, randomized, placebo-controlled, cross-over trial at 3613 m to assess the effects of Zolpidem and Zaleplon on nocturnal sleep as well as on daytime attention, fatigue and sleepiness showed no adverse effect on night time SpO_2, daytime attention levels, alertness or mood (Beaumont et al.,2007; Beaumont et al., 1996; Jouanin et al.,2009).

Conclusions: Hypnotic non-benzodiazepine drugs treat both physiological and environmental causes, seem to work without affecting respiratory drive, so sleep quality and structure were improved. With no studies describing the effects of high doses of hypnotic drugs at altitude, common sense and experience suggest high doses are inadvisable and should definitely be avoided if AMS is identified (Luks 2008).

Recommendations: Up to 3600-5000 m Temazepam (7.5-10 mg at bedtime), Zolpidem (10 mg) and Zaleplon (10 mg) are often taken for night rest without proven effects on ventilation, attention or performance but great care should be exercised in their use when combined with an early alpine start for an ascent. Recommendation Grade: 1A

Hypnotic non-benzodiazepines should be avoided in AMS. Recommendation Grade: 1B.

10. STIMULANTS

Stimulants are psychoactive drugs that induce temporary improvements in either or both mental or physical functions (Ambrose 2004). The US Anti-Doping Agency defines a stimulant as ‘a chemical agent that temporarily arouses or accelerates physiological or organic activity (The_National_Institute_on_Drug_Abuse_(NIDA) 2015). Many stimulants have a significant potential to cause drug dependency.

10.1 Generic name: **AMPHETAMINES**

Amphetamines act primarily by enhancing the brain activity of noradrenaline and dopamine, intensifying psychological sensations of alertness, concentration, and self-confidence (Cruickshank and Dyer 2009; Sulzer et al.,2005). Amphetamines are indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) and narcolepsy. The effects of amphetamine include an increase in physical energy, mental aptitude, talkativeness, restlessness, excitement, and good humour. Subjects taking amphetamine also report that they feel confident, efficient, ambitious, and that their food intake is reduced (Heal et al.,2013). Some negative effects of amphetamine (that can be dose dependent) are anxiety, indifference, slow reasoning, irresponsible behaviour, irritability, dry mouth, tremors, insomnia, and, following withdrawal, depression (Heal et al.,2013). The role of sympathomimetic drugs in the pulmonary arterial pressure response to hypoxia is well known. Amphetamines may lead to pulmonary artery hypertension due to the release of synaptic dopamine, norepinephrine and serotonin, which may cause pulmonary vasoconstriction, enhancing the risk of HAPE at altitude (van Wolferen et al.,2005).

Use in sport**:** Amphetamines enhance anaerobic performance while having little or no effect on aerobic performance. They enhance sports performance with a supplemental mental stimulus as well as effects on physical power derived from the ATP-CP, lactic acid, and aerobic energy systems (glycolysis and Krebs Cycle). Their use can carry substantial health risks of heatstroke and cardiac arrest, which have resulted in several fatalities among competitive cyclists (Logan, 2002). Amphetamines obscure pain from injuries and have enabled athletes to continue to compete whilst exacerbating injuries (Logan 2002).

10.2 Generic name: **COCAINE**

Cocaine is an extract from the leaves of the coca bush (*Erythroxylum coca*) native to South America (Biondich and Joslin 2015). Coca tea has often been recommended for travellers in the Andes. Cocaine is the most potent stimulant of natural origin (Casikar et al.,2010). Cocaine modifies the action of dopamine in the brain and this increased activation of the dopaminergic reward pathway leads to a feeling of euphoria (Barnett et al.,1981; Kuhar 1992). Physical effects of cocaine use include constricted blood vessels, dilated pupils and increased temperature, heart rate and blood pressure. It also increases motor activity (Cone et al.,1998). Complications associated with cocaine use include disturbances in hearth rhythm and heart attacks (risk of cardiac sudden death increased more than 20 –fold), chest pain and respiratory failure, strokes, seizures, headaches, and gastrointestinal complications (abdominal pain and nausea). Cocaine misuse is strongly associated with cerebrovascular accidents arising either from rupture or spasm of cerebral blood vessels (Barnett et al.,1981; Pomara et al.,2012).

Use in sport: Cocaine does not enhance performance, whether in the workplace, in sports, at school, or during sex (Braiden et al.,1994). At all doses, cocaine significantly increases glycogen degradation while increasing plasma lactate concentration without producing consistent changes in plasma catecholamine levels (Docherty 2008). A number of dramatic fatalities associated with coronary occlusion have occurred in athletes misusing cocaine who have been exercising intensely following drug administration (Kloner and Rezkalla 2003; Sordo et al.,2014). Many athletes who misuse cocaine complain of negative central effects such as perceptual misjudgements and time disorientation that reduces their athletic performance (Kloner and Rezkalla 2003; Sordo et al.,2014)..

10.3 Generic name: **CANNABINOIDS**

Cannabinoids are a class of diverse chemical compounds that act on cannabinoid receptors on cells that repress neurotransmitter release in the brain. The most notable cannabinoid is the tetrahydrocannabinol (THC), the primary psychoactive compound of cannabis (Fellermeier et al.,2001). The dried leaves and flowers of the cannabis plant are known as *marihuana*, which can be smoked or taken orally with food (baked in cookies). The resinous secretions of the plant are known as *hashish***,** which can be smoked or eaten.

Use in sport: Performance enhancing effect of cannabis is questionable. Cannabis increases resting heart rate and blood pressure, and this chronotropic effect leads to achievement of maximum heart rate at reduced workloads, decline of cardiac output and reduced psychomotor activity that have been demonstrated in many studies (Avakian et al.,1979; Lach and Schachter 1979; Renaud and Cormier 1986). On the other hand, cannabis may reduce an athlete's pre-competition stress and anxiety as a result of the euphoric effect it may produce. It has relaxing and sedative properties and improves sleep quality (Pesta et al.,2013). Its haemodynamic effects and negative psychomotor effects reduce any, positive potential effects in sports (Lorente et al.,2005; Pesta et al.,2013).

10.4 Generic name: **MESCALINE**

Mescaline or 3,4,5-trimethoxyphenethylamine is a naturally occurring psychedelic alkaloid of the phenethylamine class, known for its hallucinogenic effects similar to those of LSD and psilocybin. It shares strong structural similarities with the catecholamine, dopamine (Nichols 2004). Users typically experience visual hallucinations and radically altered states of consciousness, often experienced as pleasurable and illuminating but occasionally with feelings of anxiety or revulsion. Other effects include: open and closed eye visualizations, euphoria, dream-like state, laughter and a psychedelic experience (Monte et al.,1997). Side effects of mescaline use may include anxiety, tachycardia, dizziness, diarrhoea, vomiting and headache (Monte et al.1997).

Stimulants at altitude: Stimulant drugs have a long story in the mountains. Anecdotal accounts suggest that many ascents of 8000 m peaks in the 1950s were done with the use amphetamines (Pervitin = methylamphetamine). A 1993 study in the Austrian Alps found amphetamines in the urine of 7.1% of mountaineers going above 3300 m (Roggla et al.,1993). WADA have reported international top class competition climbers testing positive for both amphetamines and cocaine (Boghosian et al.,2011). At high altitude central effects of stimulants such as perceptual misjudgements and time disorientation may cause life-threatening risks for a mountaineer (Roggla et al.,1993). Coca derived products are commonly recommended for prophylaxis for travellers in the Andes and anecdotal reports suggest they are now also being used by trekkers in Asia and Africa. Their use in prevention of AMS has never been systematically studied, and they should not be substituted for other established preventive measures (Luks et al.,2014). Only one small study suggests that chewing coca leaves may be beneficial during exercise and that the effects are felt over a prolonged period of sustained physical activity (Braiden et al.,1994).

Stimulants and doping: A total of 62 stimulants (from 61 chemical entities) are listed in the WADA list. Many of these compounds are old agents, with research going back to the 1950s and 1960s, long before modern techniques and knowledge of receptor subtypes were studied in detail (Boghosian et al.,2011; WADA 2016b). All stimulants are prohibited, except substances included in the 2016 Monitoring Program (caffeine, nicotine, etc). Due to the transient advantage they give in nature, stimulants are prohibited *in-competition* only, this means that an athlete who is not competing does not need to obtain a TUE (Therapeutic Use Exemption) in order to use these drugs (WADA 2016b).

Conclusions: The risk of overexertion is high when using stimulants. This may result in exhaustion, hypothermia, collapse and death. Euphoric effects of stimulants may lead to poor decision-making resulting in mountain accidents.

Recommendations: Stimulants should not be used during mountaineering as they reduce attention and may increase the chances of risk-taking and exhaustion. Recommendation Grade: 1B. Benefits for acclimatization are unproven. Recommendation Grade: 1C

11. ANALGESICS

There are many painkillers available, some of them are suitable for use by a lay person in the wilderness and taken alone or in combination they will safely treat nearly all painful conditions (e.g. ASA, Ibuprofen, Acetaminophen). The strongest painkillers (opioids) need specific training for their use.

NON-OPIOID ANALGESICS

Headache is known to be the predominant symptom in AMS, which is also frequently accompanied by nausea, vomiting and insomnia. At altitudes between 2500 m and 5000 m about 20-90% of those who are not acclimatised will experience this problem. Headache is an essential symptom in the current diagnosis of AMS (Richalet et al.,1991; Roach et al.,2011), but West (West 2011) argues that there are some people who suffer from acute altitude-related symptoms but do not have a headache. High altitude headache is a different entity (Gertsch et al.,2010). The differential diagnosis of headache at high altitude is complex (Küpper et al.,2012). Both AMS and high altitude headache can be simulated by other conditions, such as migraine that are not necessarily related to altitude exposure (Young et al.,1996). Analgesic, e.g. Acetylsalicylic acid and Ibuprofen, are frequently used by subjects suffering from migraine (Broome et al.,1994; Burtscher et al.1998). Consequently serotonin-receptor agonists, specifically effective for treatment of migraine (Sumatriptan), or drugs normally used to control neuropathic pain, epilepsy and as an unlicensed drug for migraine control (Gabapentin) have been studied for treatment of AMS headache.

11.1 Generic name: **ACETYLSALICYLIC ACID**

Acetylsalicylic acid irreversibly inhibits cyclooxygenase -1 and -2 (COX-1 and -2) enzymes, via acetylation, which results in decreased formation of prostaglandin precursors; this inhibits formation of prostaglandin derivate, thromboxane A_2 via acetylation of platelet cyclooxygenase, thus inhibiting platelet aggregation (Vane and Botting, 2003). Many adverse effects are dose related and dependent on patient susceptibility. Extensive side effects encompassing cardio-circulatory function, lungs, gastrointestinal system (6-31%), skin and hair are reported (American_Pharmacists_Association, 2012).

At altitude: Burtscher showed the efficacy of Acetylsalicylic acid as prophylaxis against headache when mostly resting during acute high-altitude exposure (320 mg Acetylsalicylic acid, 1 tablet every 4 hours, starting 1 hour before arrival at 3480 m altitude and then after 3 and 7 h after arrival) (Burtscher et al., 1998). Acetylsalicylic acid probably prevented high-altitude headache since acute hypoxia augments prostaglandin concentration and prostaglandins increase. In a second study (Burtscher et al.,2001) using the same drug protocol Acetylsalicylic acid reduced the incidence of headache when exercising during acute altitude exposure: climbers were transported to an altitude of 3000 m and then climbed up to 3800 m. Afterwards they descended to a mountain hut at 3480 m and spent two nights there. Its antiplatelet effect increases the risk of internal bleeding, which could be further increased if combined with Dexamethasone (i.e. gastrointestinal bleeding) (Vane and Botting 2003; Wu and Liu 2006; Wu et al.,2007). The potential benefit in reducing clotting at high altitude to prevent the risk of venous thrombosis is negligible (Stovitz and Johnson 2003).

11.2 Generic name: **IBUPROFEN**

Ibuprofen reversibly inhibits cyclooxygenase-1 and -2 (COX-1 and -2) enzymes, which results in decreased formation of prostaglandin precursors (American_Pharmacists_Association 2012).

At altitude: Two prospective double blind, placebo controlled studies (Gertsch et al.,2012; Lipman et al.,2012) have evaluated the use of Ibuprofen, for prevention of acute mountain sickness. The authors of both studies cite the importance of inflammation in the pathophysiology of AMS (Julian et al.,2011; Olesen 1994; Tissot van Patot et al.,2005) as supporting evidence that a non-steroidal anti-inflammatory drug (NSAID) should be of benefit in preventing AMS. As the authors point out, this favours the conclusion that Ibuprofen acts to prevent the constellation of symptoms rather than just treating the headache. Another study comparing Acetaminophen (i.e. acetaminophen 1000 mg) with Ibuprofen (400 mg) for the prevention of AMS might shed light on the relative importance of anti-headache and anti-inflammatory effects because Acetaminophen has no significant anti-inflammatory effect but is effective against headache (Harris et al.,2003). Ibuprofen does carry potentially serious risks such as gastrointestinal hemorrhagic (Van Wijck et al.,2012), but tends to have fewer overall side effects than Acetazolamide. Unlike Dexamethasone, it does not cause euphoria or decrease nausea. Its analgesic and anti-headache properties are limited and unlikely to mask significant symptoms (Broome et al.,1994). The fact, that it is widely available without a prescription makes it an attractive option for prevention of AMS. Current evidence suggests that Ibuprofen is effective in the prevention of AMS and that its benefit is not limited to preventing headache. It is likely that ibuprofen acts by decreasing inflammatory responses to hypoxia (Zafren 2012). Ibuprofen is used to mask soft tissue pain in endurance mountain marathon runners and sport climbers (Nieman et al.,2006; Stovitz and Johnson 2003), but it aggravates exercise-induced small intestinal injury in 20% of healthy endurance athletes (Van Wijck et al.,2012).

11.3 Generic name: **SUMATRIPTAN**

Selective agonist of serotonin (5-HT_{1B} and 5-HT_{1D} receptors) in cerebral arteries, Sumatriptan causes vasoconstriction and reduces neurogenic inflammation associated with antidromic neuronal transmission correlating with relief of migraine (American_Pharmacists_Association 2012).

At altitude: Three reports suggest the efficacy of Sumatriptan for the treatment of high altitude headache (Bartsch et al.,1994; Jafarian et al.,2007b; Utiger et al.,2002). A randomized, placebo-controlled double-blind trial performed at 4559 m on 29 mountaineers receiving 100 mg orally, noted a significant decrease of headache scores one and three hours after administration but not after 12 hours, concluding its possible use only for a transient amelioration of headache (Utiger et al.,2002). Jafarian et al. conducted a prospective, double blind, randomized, placebo-controlled clinical trial, in 102 subjects at 3500 m within 24 h of ascent. Sumatriptan 50 mg was effective to prevent AMS development (Jafarian et al.,2007b). In 9 subjects at 4559 m 100 mg of Sumatriptan reduced the headache score from mean 2.8 to 0.8 ($p<0.01$, Wilcoxon signed rank test) (Bartsch et al.,1994).

Burtscher, in a randomized, double-blind trial (33 subjects at 3480 m, Sumatriptan 100 mg or Ibuprofen 600 mg), showed that Ibuprofen but not Sumatriptan was effective for high-altitude headache (nearly complete relief in the Ibuprofen group, no decrease of the score in the other group) (Burtscher et al.,1995).

11.4. Generic name: **GABAPENTIN**

Gabapentin is structurally related to GABA. Gabapentin modulates the action of glutamate decarboxylase (GAD) and branched chain aminotransferase (BCAT), two enzymes involved in GABA biosynthesis. In human and rat studies, Gabapentin was found to increase GABA biosynthesis, and to increase non-synaptic GABA neurotransmission *in vitro* (Petrucci et al.,2016).

At altitude: Two studies were performed at 3500 m to evaluate the treatment of Gabapentin on altitude headache (Jafarian et al.,2008; Jafarian et al.,2007a). The first was on 12 subjects at an altitude of 3500 m receiving 300 mg of Gabapentin and 12 placebo. Nine subjects of the placebo group asked for additional analgesia. The mean headache-free period in Gabapentin group was 17.1 h, significantly longer than in the placebo group (10.1 h). The second study was on 204 un-acclimatised subjects aged 15-65 year, at the same altitude, assigned randomly to 600 mg single-dose of Gabapentin or placebo. The incidence of headache was the same but the severity of headache was lower in the Gabapentin group with acceptable tolerability. The drug's side effect profile would put most climbers off using it (including dizziness, somnolence, fatigue, paraesthesia) (American_Pharmacists_Association, 2012).

Doping: The four mentioned analgesics are not included in WADA list of prohibited agents.

Conclusions: There are several ways to prevent AMS when going to high altitude. The most reliable and safest method is gradual ascent to allow time for acclimatization. In an extensive EBM review from 2000 to 2011 (Seupaul et al.,2012) different studies have reported reduction in the incidence of AMS with the use of Gabapentin or Sumatriptan and have showed that Ibuprofen is effective in the prevention of AMS and not limited to preventing headache. It is likely that primary effect of Acetylsalicylic acid may simply be on headache control rather than true prevention of AMS. A greater beneficial effect may be achieved by the combined application of Acetazolamide and Acetylsalicylic acid (Basnyat et al.,2008a). This combination increases oxygenation and reduces prostaglandin synthesis but the adverse effects of Acetylsalicylic acid should not be underestimated.

Recommendations: Acetylsalicylic acid (320 mg every 4 h for a total of three doses) or Ibuprofen (400 or 600 mg once, may be repeated) may be used in the prevention and in the treatment of high altitude AMS related headache. Recommendation Grade: 1A.

Side effects of non-opioid analgesics should be considered (e.g. internal bleeding). Gastrointestinal bleeding risks are higher when combined with Dexamethasone or simply when at high altitude. Recommendation Grade: 1B.

Gabapentin (300mg) and Sumatriptan (50-100 mg prior to ascent) may help prevent AMS, Recommendation Grade: 2B.

OPIOIDS

Opioids are a group of drugs that are used for treating pain. They are derived from opium, which comes from the poppy plant (*Papaver somniferum)*.

11.5 Generic name: **MORPHINE**

Morphine binds to opioid receptors in the central nervous system, causing inhibition of ascending pain pathways, altering the perception of and response to pain, producing generalized central nervous system depression (American_Pharmacists_Association, 2012; Busch-Dienstfertig and Stein, 2010).

11.6 Generic name: **CODEINE**

Codeine or 3-methylmorphine is a naturally occurring methylated morphine, with the same mechanism of action (Busch-Dienstfertig and Stein, 2010).

11.7 Generic name: **TRAMADOL**

Tramadol and its active metabolite (M1) bind to μ-opiate receptors in the CNS causing inhibition of ascending pain pathways, altering the perception of and response to pain. It also inhibits the reuptake of norepinephrine and serotonin, which also modifies the ascending pain pathway (American_Pharmacists_Association, 2012).

At altitude: Opioids should be avoided during acute altitude exposure or illness due to their respiratory depressant effects (Teichtahl and Wang, 2007). Respiratory side effects are exacerbated with alcohol, sedatives, sleeping pills, sedating antihistamines, or prochlorperazine (Gudin et al.,2013). Tramadol has a less depressant effect on respiration than the other opioids (Rojas-Corrales et al.,1998). The theoretical possibility of developing HAPE as a result of a hypoxic increased pulmonary-capillary hydrostatic pressure and an increased pulmonary capillary permeability due to hypoxaemia, potent histamine release and respiratory acidosis caused by depression of medullary respiratory centers must be taken in account (Radke et al., 2014). There is no HAPE recorded in FDA reports in 38699 people who have side effects while taking Tramadol (eHealthMe 2016). Central sleep apnoea is induced by the use of opioids. In 2007 a study conducted at an elevation of 1500 m showed a dose-dependent relationship between chronic opioid use and the development of specific central sleep apnoeas and ataxic breathing (Gudin et al.,2013). Constipation is a common side effect of opioids so a laxative must be given if more than a few doses are taken. Only consider opioids for abdominal pain if constipation has been excluded, and the victim is moving his bowels normally due to the risk for paralytic ileus (Dubowitz 1998; Duff and Gormly 2012). In a 1969 comparison Carson showed that codeine 132 mg was less efficacious than a placebo in the prevention of AMS (Dumont et al.,2000). Opioids should be used with extreme caution in patients with head injury (American_Pharmacists_Association, 2012).

High altitude dry cough is associated with inflamed mucous membranes in the respiratory tract. Codeine containing preparations may be of some limited value as a cough suppressant (Duff and Gormly 2012).

Doping: All opioids are included in the list of WADA substances and methods prohibited *in-competition* (WADA 2016b).

Conclusions: At altitude >2500 m any medication that depresses respiration may make AMS, HACE and HAPE more likely or worse. Most reviews conclude that opioids produce impairment of human performance on tests of sensory, motor, or attention abilities, and can bring excessive risks, with very little advantage. The only ethical medical use is for treatment of severe pain (Tramadol 50 mg tablets 1-2 every 4 h, up to maximum 400 mg per 24 h or Codeine 30 mg 1-2 tablets every 4 h as needed) (Duff and Gormly 2012).

Note: Opioids are illegal in many countries, even in transit. Carry appropriate Custom’s forms. Check country requirements with relevant government departments.

Recommendations: Opioids should not be used for exertional purposes. Recommendation Grade: 1B

Opioids should be considered in the treatment of severe pain. Recommendation Grade: 1A

12. VASODILATORS

12.1 Generic name**: NIFEDIPINE**

Nifedipine is a dihydropyridine calcium channel blocker (CCB) that primarily blocks L-type calcium channels. It works by affecting the movement of calcium into the cells of the heart and blood vessels. Nifedipine inhibits the spasm of the coronary artery and dilates the systemic arteries, resulting in a increase of myocardial oxygen supply reducing its workload. The vasodilatory effects of Nifedipine result in an overall decrease in blood pressure. It is also used for the small subset of pulmonary hypertension patients whose symptoms respond to calcium channel blockers. Headache (10-23%), peripheral oedema (7-30%), dizziness (10-27%), flushing (10-25%), nausea and heartburn (10%) are the most important side effects. Symptoms of overdose include dizziness, drowsiness, nausea, severe drop in blood pressure, slurred speech, and weakness. The rapid reduction in blood pressure may precipitate adverse cardiovascular events and peripheral oedema may lead to an increased risk of frostbite. Alcohol may increase central nervous system depression and may increase the effects of Nifedipine. Natural licorice and grapefruit in all forms (e.g. whole fruit, juice or rind) can significantly increase levels of Nifedipine, may cause toxicity and should be avoided (American_Pharmacists_Association 2012; Kulhmann et al.,1986; Ramsch et al.,1986).

At altitude: Nifedipine effectively lowers hypoxic pulmonary hypertension and improves gas-exchange in patients with HAPE. This results in regression of alveolar and interstitial oedema (Simonneau et al.,1981). For its arterial pulmonary vasodilatory effect, Nifedipine is cheap, effective, lifesaving, and the drug of choice in the treatment of HAPE (Luks et al.,2014; Luks and Swenson 2008; Maggiorini 2010; Oelz et al.,1989; Oelz et al.,1991; Oelz et al.,1992). In mountaineers with HAPE at 4559 m, treatment with 20 mg slow-release Nifedipine taken every 6 h led to a persistent relief of symptoms, improvement of gas exchange, and radiographic clearance over an observational period of 34 h. In this study, Nifedipine therapy was not associated with hypotension (Maggiorini,2006).

Being effective in the treatment of increased pulmonary artery pressure during acute high altitude exposure, Nifedipine may have a role in the prevention of HAPE in susceptible individuals (Bartsch et al.,1991). 20 mg Nifedipine of the slow-release formulation taken every 8 h starting 24 h before ascent to 4559 m and continued until descent decreased the incidence of HAPE from 63% to 10% (Maggiorini 2006).

If symptoms are present despite Nifedipine prevention, prophylaxis with Acetazolamide is recommended (Basnyat et al.,2003; Greene et al.,1981). Whether Acetazolamide prophylaxis prevents HAPE is yet unknown, although Acetazolamide inhibited hypoxic pulmonary vasoconstriction in animals (Berg et al.,2004; Hohne et al.,2004) but failed to do the same in a large study of partially acclimatized humans in the Everest region (Basnyat et al.,2008b).

Nifedipine does not treat or prevent AMS. Many studies demonstrated that lowering pulmonary artery pressure has no beneficial effects on gas exchange and symptoms of AMS (Hohenhaus et al.,1994; Maggiorini et al.,2006). Its use in high altitude medicine should be limited to prevention and treatment of HAPE and if used for prevention it cannot then be used for treatment (Hohenhaus et al.,1994). For treatment, first check that the patient is not already on hypertension therapy with a calcium channel blocker (CCB). Marked hypotension may be precipitated if used in very dehydrated patients or those receiving other antihypertensive drugs (PDE-5I, Beta-blockers, Alfa-blockers, others CCB) (Donegani et al.,2014). At altitude slow-release preparations should be preferably used. If the patient is semi conscious but swallowing the Nifedipine capsule (10 mg) may be pierced and the liquid squirted into his mouth (use with caution); blood pressure lowering should be done at a rate appropriate for the patient’s conditions (Luks and Swenson 2008). NOTE: Although often stated to the contrary the patient must be able to swallow, otherwise the drug will have no effect (van Harten et al.,1987).

Note: Management of pulmonary hypertension, prevention and treatment of HAPE is an off-license use (American_Pharmacists_Association 2012; Kulhmann et al.,1986).

Doping: Nifedipine is not included in WADA prohibited list.

Conclusions: Nifedipine can be used specifically for treatment of severe HAPE to buy time for the vital life-saving descent. In specific cases it may be used for prevention to minimise the risk of HAPE developing.

12.2 PHOSPHODIESTERASES

The two major PDE5 inhibitors (PDE5-I) for mountain sport purposes are Sildenafil and Tadalafil.

Generic name: **SILDENAFIL, TADALAFIL**

Both Sildenafil and Tadalafil are primarily used to treat erectile dysfunction but are also effective in the treatment of pulmonary arterial hypertension. They relax the arterial wall, leading to decreased pulmonary arterial resistance and pressure. This, in turn, reduces the workload of the right ventricle of the heart and improves symptoms of right-sided heart failure (Jeon et al.,2005; Kirsch et al.,2008; Sakuma et al.,2008; Wang et al.,2012). Side effects include: headache (16-46%), epistaxis (9-13%), dyspepsia (7-17%), flushing (10%), insomnia (7%), myalgia (7%), exacerbated dyspnoea (7%), abnormal vision (colour changes, blurred vision or increased sensitivity to light (3-11%), diarrhoea (3-9%), erythema (6%) (American_Pharmacists_Association 2012). In the same trial several participants reported "feeling subjectively more fatigued and unable to mentally focus during exercise while on active drug treatment" (Hsu et al.,2006). Blood pressure may drop due to vasodilator effects (Cheitlin et al.,1999; Chrysant 2013). Concurrent use with alpha-adrenergic antagonist therapy or substantial alcohol consumption may cause symptomatic hypotension. Avoid concomitant use with organic nitrate vasodilators and be careful if combined with calcium channel blockers. Substantial consumption of ethanol may increase the risk of hypotension and grapefruit may increase serum levels to toxic levels (American_Pharmacists_Association 2012).

At altitude: A limited number of studies have evaluated the use of the PDE5-I as preventive/therapeutic agents for mountain sickness (Fagenholz et al.,2007; Jouanin et al.,2009; Kleinsasser and Loeckinger 2002; Maggiorini et al.,2006). PDE5-I are not effective in preventing AMS (Jouanin et al.,2009; Maggiorini 2006). In some susceptible individuals PDE5-I may possibly exacerbate AMS by unknown mechanism (Ghofrani et al.,2004).

Prevention of HAPE: Prevention of HAPE in individuals with a positive history of HAPE could be obtained using 10 mg Tadalafil bid: the incidence of HAPE was 74% in the placebo and 10% in the Tadalafil group (randomized, placebo-controlled trial, at 4559 m., 8 subjects, $p<0.007$ vs. placebo) (Maggiorini et al.,2006). The number of individuals in the study was small and extensive clinical experience with the medication is lacking when compared to Nifedipine. Regardless, In the WMS's guidelines for the prevention and treatment of altitude illness Sildenafil and Tadalafil, with its longer half-life, are recommended only for HAPE prevention (Luks et al.,2014).

Treatment of HAPE: By virtue of their ability to cause pulmonary vasodilation and decrease pulmonary artery pressure, there is a strong rationale for using PDE5-Is in HAPE treatment (Jin et al., 2010; Kirsch et al.,2008), but to date there are no clinical trials on the use of more selective pulmonary vasodilators such as Sildenafil or other phosphodiesterase-5 inhibitors for HAPE treatment (Maggiorini 2006). In one small study (Fagenholz et al.,s 2007), 11 patients were treated for HAPE at 4.240m in Nepal using concomitant drugs (Nifedipine and Acetazolamide in all, Sildenafil in most).

Altitude-induced hypoxia can cause severe decrements in submaximal and maximal exercise performance. These decrements can be attributed in part to a ventilation-perfusion mismatch. Strategies to reduce pulmonary hypertension in hypoxia would be predicted to improve oxygen diffusion and arterial oxygen saturation (SaO_2), cardiac output and exercise performance (Salisbury and

Hawley, 2011). Richalet (Richalet et al.,2005) and Faoro (Faoro et al.,2007) observed an increase of exercise SaO_2 after 3 days of treatment. Bates (Bates et al.,2011) showed a trend toward higher SaO_2 at day 1 but any difference between treatment and control group for up to 7 days. On the contrary, Xu (Xu et al.,2014) showed that short-term treatment attenuated the pulmonary systolic arterial pressure but had no significant beneficial effects on SaO_2, heart rate and AMS. Other studies have investigated the effects of PDE5-I on exercise performance at altitude (Aldashev et al.,2005; Ghofrani et al.,2004; Hsu et al.,2006; Perimenis 2005; Reichenberger et al.,2007; Ricart et al.,2005; Richalet et al.,2005; Zhao et al., 2001) and these studies showed that certain individuals can benefit from Sildenafil use during acute hypoxia, but not normoxia, in terms of cardiac output, arterial saturation and exercise performance (Di Luigi et al.,2008).

Doping: Sildenafil and Tadalafil (PDE5-I) are not included in WADA prohibited list.

Conclusions: Currently limited data and experience at altitude with side effects that could be potentially dangerous at altitude. PDE5-1s should be used with caution at altitude.

Recommendations: Prevention of AMS. Both Nifedipine and Tadalafil are not effective in preventing AMS.

Prevention of HAPE: Nifedipine: 30 mg slow release twice daily or 20 mg of slow release every 8 hours, without loading dose (Bartsch et al.,1991) (Luks et al.,2014). Recommendation Grade: 1B

Sildenafil: 50 mg every 8 hours or Tadalafil: 10 mg twice daily. Recomendation Grade 1C.

Adding Acetazolamide (125 mg twice daily) may further increase HAPE prophylaxis. Recommendation Grade: 2C

Treatment of HAPE: Nifedipine: 30 mg slow release every 12 hours or 20 mg of slow release every 6-8 hours (Oelz et al.,1989). Recommendation Grade: 1B (in adjunct to vital descent).

Do not use PDE5-I for treatment of HAPE. Recommendation Grade: 1B.

13. XANTHINE ALKALOIDS

Xanthine (3,7-dihydro-purine-2,6-dione), is a purine base found in many living tissues. A number of stimulants are derived from xanthine, including theophylline, caffeine (also known as theine, found in coffee beans and tea leaves) and theobromine (found in cocoa and derivatives) (Rall 1980). Derivatives of xanthine (known collectively as xanthines) are a group of alkaloids commonly used for their effects as mild stimulants and as bronchodilators (Fredholm 1985; Rall 1980). Methylated xanthines (i.e. methylxanthines) affect not only the airways but stimulate heart rate, force of contraction causing cardiac arrhythmias at high concentrations. Toxicity can also lead to convulsions that are resistant to anticonvulsants. Methylxanthines induce acid and pepsin secretion in the GI tract. Methylxanthines are metabolized in the liver (Fredholm 1985).

13.1 Generic Name: **CAFFEINE**

Caffeine is a psychoactive drug whose stimulants properties depend on its ability to block adenosine transmission in the brain. Caffeine has vasoconstriction properties, antagonizing adenosine receptors in the blood vessels and reducing adenosine-mediated vasodilatation, thereby decreasing cerebral blood flow, myocardial blood flow and exercise-induced myocardial flow reserve (Namdar et al., 2006; Umemura et al.,2006). Caffeine stimulates ventilation increasing hypoxic ventilatory response, hypercapnic ventilatory response, and thus ventilatory response to exercise. Additionally caffeine increases resting ventilation and metabolic rate (Chapman and Stager 2008; American_Pharmacists_Association 2012; Fisone et al.,2004; Lorino et al.,2006). Caffeine can improve exercise performance at low altitudes (Richardson and Clarke 2016; Fernandez-Elias et al.,2015; Diaz-Laraet al.,2016; An et al.,2014). The mechanism is both central with reduced perceived exertion and peripheral with increased muscular force from changes in calcium utilization, stimulating the release of calcium ions from the sarcoplasmic reticulum (Burke 2008; Davis and

Green 2009; Goldstein et al.,2010;Graham 2001; Paluska 2003; Woolf et al., 2008). Side effects: palpitations, sinus and supraventricular tachycardia, arrhythmias, angina, flushing; agitation, dizziness, delirium, hallucinations, insomnia, irritability, restlessness, psychosis; urticaria; oesophageal sphincter tone decreased, gastritis; fasciculations. Intraocular pressure increase, miosis. Diuresis is increased (American_Pharmacists_Association 2012; WADA 2016b).

Typical caffeine contents of commonly consumed beverages (Hackett 2010):

Instant coffee (8oz (1oz = 30ml) cup) 40-110 mg, coffee espresso (2oz cup) 100 mg, black tea (8oz cup) 50 mg, green tea (8oz cup) 30 mg, Coca Cola (12oz can) 34 mg, Pepsi Cola (12oz can) 38 mg, Red Bull (8oz can) 80 mg.

Caffeine and theine are chemically identical; the only thing that sets them apart is the concentration, lesser in a cup of tea than in a cup of coffee. Tea is the most widely consumed beverage in the world after water. Tea is known to be a rich source of caffeine, flavonoid antioxidants (oxidized polyphenols) and also contains a unique amino acid, L-theanine that may modulate aspects of brain function in humans. One randomised, placebo-controlled, double-blind, balanced crossover study investigated the acute cognitive and mood effects of L-theanine (250 mg), and caffeine (150 mg), in isolation and in combination. The results suggest that beverages containing L-theanine and caffeine show a significant positive interaction and may have more pronounced cognitive effects to those containing caffeine alone (faster simple reaction time, faster numeric working memory reaction time and improved sentence verification accuracy) (Haskell et al.,2008).

Also other data indicate that L-theanine has a significant positive effect on the general state of mental alertness or arousal (Bryan 2008; Camfield et al., 2014; Nobre et al., 2008; Scott et al., 2004).

At altitude: Because of its capacity to reduce cerebral vasodilation in response to hypoxia owing to its vasoconstriction properties, caffeine will help prevent or treat altitude headaches and therefore AMS. In addition, at high altitude it may improve sleep by reducing episodes of oxygen desaturation. Caffeine reduces cerebral blood flow and the ratio of cerebral blood flow to cerebral metabolic rate for oxygen. Caffeine stimulates ventilation and this effect could be more pronounced where ventilation is already markedly increased, and therefore at high altitude this may be helpful. Studies of caffeine and exercise are limited, but they suggest that caffeine might confer more benefit to performance at high altitude than at sea level and do not suggest that it might impair exercise. Caffeine does have diuretic effects but with normal consumption, even in an environment of cold and altitude where diuresis is stimulated, caffeine did not increase diuresis with no risk for dehydration (Hackett 2010). A study performed by Scott et al. showed that there is no evidence that tea acts as a diuretic, when drunk by regular tea drinkers at altitude but it does have a positive effect on mood (Scott et al., 2004). It also did not increase the altitude-induced increase of heart rate significantly.

Caffeine may interfere with sleep and promotes wakefulness, so it is recommended avoiding caffeine in the late afternoon or evening, especially in non-habitual users, to avoid caffeine-induced insomnia which could aggravate altitude-associated insomnia (Hackett 2010). Habitual caffeine users should not discontinue it because of travel to altitude since withdrawal symptoms are very similar to those of AMS (Hackett 2010).

Doping: Caffeine was removed from the WADA Prohibited List in January 2004 since it is present in a wide range of popular foods, metabolized at very different rates in individuals with different urinary concentrations, which do not always correlate with the dose ingested. In 2012, following concerns raised by some sport physiologists, WADA included caffeine in the 2012 Monitoring Program to monitor potential misuse in sport, keeping the situation ‘under review’ (WADA 2016b).

Conclusions: Even at physiological doses (3-6 mg/kg) caffeine provides an ergogenic aid especially in endurance events. It has peripheral effect targeting muscle metabolism as well as a central effect on the brain to enhance performance, which is also relevant for anaerobic performance.

Post-exercise caffeine intake seems to benefit recovery by increasing rates of glycogen re-synthesis.

Recommendations: Caffeine (1.5-3 mg/kg) may help exercise performance at altitude. Recommendation Grade: 1B.

13.2 Generic Name: **THEOPHYLLINE**

Theophylline is a drug used for respiratory diseases such as COPD and asthma. As a xanthine it bears structural and pharmacological similarity to caffeine and theobromine (Scott et al.,2004). Theophylline is naturally found in cocoa beans. Trace amounts are also found in brewed tea. Theophylline causes bronchodilation, diuresis, CNS and cardiac stimulation, and increased gastric acid secretion (Essayan 2001; Schultze-Werninghaus and Meier-Sydow 1982). The metabolic effect of theophylline was studied (Greer, 2000) demonstrating that this substance is ergogenic independent of muscle glycogen (Pigozzi et al.,2003). Adverse effects observed at therapeutic serum levels include: tachycardia and flutter, hyperactivity, insomnia, restlessness, seizures, tremor, hypocalcaemia (with concomitant hyperthyroidism), nausea, vomiting, gastric reflux, difficulty urinating (elderly males with prostatism), increased diuresis (American_Pharmacists_Association 2012). **At altitude**: Theophylline at low dose (300 mg daily) is known to significantly reduce AMS symptoms at altitude (Kupper et al.,2008b). The mechanism found for the beneficial effect is most likely related to stimulation of respiratory drive reducing the frequency of oxygen desaturation during sleep (Fischer et al.,2004; Kupper et al.,2008b). Additional effects of theophylline on AMS symptoms may include a decrease in adenosine-mediated cerebral blood flow or a reduction in inflammatory responses and vascular permeability as a result of its phosphodiesterase inhibitor activity. There is also no evidence that theophylline increases significantly the heart rate at altitude (Kupper et al.,2008b). If combined with dehydration, alcohol, smoking or even viral illness even a low dose of Theophylline (250 mg slow release) can lead to potentially dangerous toxicity (Fischer et al., 2000), although such problems were never observed at altitude so far (Fischer et al., 2004; Kupper et al.,2008b). This drug has multiple interactions with other drugs and a narrow therapeutic range. With Acetazolamide, Theophylline can decrease the potassium level in the blood and if combined with Azithromycin, which is often used to treat traveller's diarrhoea, it can easily reach toxic levels (American_Pharmacists_Association 2012).

Doping: Theophylline has been discussed at WADA since 2003 but it is not prohibited although it increases performance at sea level (WADA 2016b) .

Conclusions: Theophylline could be considered an alternative to reduce AMS symptoms in those intolerant of Acetazolamide but it has potential side effects, many drug interactions and a narrow therapeutic range.

Recommendations: Low-dose, slow-release theophylline (300 mg) may be used to reduce symptoms of AMS in association with alleviation of events of periodic breathing and oxygen desaturations. Recommendation Grade: 1B.

14. MELDONIUM

Meldonium, also known as *Quaterine*, *MET-88*, and *THP* is a limited-market pharmaceutical, developed in 1970. It is distributed in Eastern European countries as an anti-ischemia medication. It is not approved in most Western countries. Meldonium is used to treat angina and myocardial infarction (Hayashi et al.,2000; Dzerve et al.,2010; Sesti et al.,2006). It acts by reducing damage to cells that can be caused by some products of carnitine. It reduces, presumably, by inhibiting the enzyme γ-butyrobetaine hydroxylase in the carnitine biosynthetic pathway. γ-butyrobetaine hydroxylase belongs to the 2-oxoglutarate oxygenase superfamily and catalyses the formation of L-carnitine from γ-butyrobetaine (Jaudzems et al., 2009; Liepinsh et al., 2006). Recent studies argued that Meldonium "demonstrates an increase in endurance performance of athletes, improved rehabilitation after exercise, protection against stress, and enhanced activations of central nervous system (CNS) functions" (Dzintare and Kalvins 2012; Gorgens et al.,2015). Ninety day administration of Meldonium improved sexual performance and sperm motility of boars and it also increased concentration of testosterone in blood serum (Bruveris et al.,2013).

At altitude. No data available.

Doping. Since January 1st 2016, Meldonium has been on the World Anti-Doping Agency (WADA) list of substances banned from use by athletes. WADA classes the drug as a metabolic modulator, just as it does insulin (WADA 2016b). However, there are debates over its use as an athletic performance enhancer. Some athletes are known to have been using it prior to its ban. In March 2016, WADA made a partial retraction on Meldonium (WADA 2016a). WADA admitted that there is only limited data on how quickly the drug is cleared from the human body. It was found that low levels of the drug could show up in an athlete's urine for "a few months", meaning some positives could have been the result of the athlete using the drug before it was banned. Based on preliminary data and awaiting ongoing studies WADA stated that if the urine level of the drug was < 1 ug/ml, the result is "compatible with an intake prior to January 2016", and the responsible anti-doping agency could clear the athlete. Other levels were adjusted to allow for a potentially long wash out period.

Conclusion. No data whether this substance might be of a benefit or harm or how it might work in hypoxia.

Recommendations. Meldonium should not be used at any time by any mountaineer. Recommendation Grade: Expert opinion.

CONCLUSIONS

Drugs have been and are being used in the mountaineering community. Some essential drugs can be lifesaving in a medical emergency. There is also good evidence that some drugs can be beneficial at altitude, or even for low altitude climbing, but many drugs are used by climbers to enhance performance based on very poor evidence and unverified rumour. In many cases the drug itself is unproven, its effects at physiological extremes are untested and there is a risk of side effects or interactions. Even with “proven” drugs the small size of most high altitude studies results in poor quality evidence. We hope that this review will help people make informed decisions when working with their mountain medicine physician. Although the ethics of drug use in the mountains are a personal decision we believe that all mountaineers should be open about any artificial aids, including drugs, used for any ascent.

Table 1. Classification scheme for grading evidence (Guyatt et al.,2006)

Grade 1A	Strong recommendation, high quality evidence benefits clearly outweigh risks and burden or vice versa
Grade 1B	Strong recommendation, moderate-quality evidence benefits clearly outweigh risks and burdens or vice versa
Grade 1C	Strong recommendation, low-quality or very low-quality evidence benefits clearly outweigh risks and burdens or vice versa
Grade 2A	Weak recommendation, high-quality evidence benefits closely balanced with risks and burdens
Grade 2B	Weak recommendation, moderate-quality evidence benefits closely balanced with risks and burdens
Grade 2C	Weak recommendation, low-quality or very low-quality evidence, uncertainty in the estimates of benefits, risks and burden; benefits, risk and burden may be closely balanced

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